# A RANDOMIZED CONTROLLED CLINICAL TRIAL

# TO COMPARE THE SAFETY AND EFFICACY

# OF MITOMYCIN C AND OLOGEN

# IN PATIENTS UNDERGOING

# PHACOTRABECULECTOMY

**Christian Medical College, Vellore** **Dr. Smita Dikshit**

# BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "A randomized controlled trial to compare the safety and efficacy of Mitomycin C and Ologen in patients undergoing phacotrabeculectomy" done towards fulfillment of the requirements of the Tamil Nadu Dr. MGR Medical University, Chennai, for the MS Branch III (Ophthalmology) examination to be conducted in March 2013, is a bona fide work of Dr. Smita Dikshit, postgraduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

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1 INTRODUCTION As per the data of World Health Organization in 2010 1 there are 39 million people blind in the whole world. 20.5% of these patients are in India which is the second highest, next to China. Glaucoma accounts for second most common cause of blindness, second only to cataract 1 . The only modifiable risk factor for preventing the progression of glaucoma is IOP. It can be controlled by different modalities of treatment which includes medications, laser treatment and surgery. Surgery is indicated if IOP is not controlled on maximal tolerated antiglaucoma medications, when patient is non compliant, patient cannot afford medications (which is common in developing country like ours),...

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# INTRODUCTION

According to World Health Organization (WHO) (1) there are 39 million people blind in 2010 in the whole world. 20.5% of these patients are in India which is the second highest, next to China. Glaucoma accounts for second most common cause of blindness, second only to cataract[1].

The only modifiable risk factor in preventing the progression of glaucoma is Intra Ocular Pressure (IOP). IOP can be reduced by different modalities of treatment which includes medications, laser treatment and surgery. Surgery is indicated if IOP is not controlled on maximal medical therapy with antiglaucoma medications and when compliance and affordability are issues. Co-existing cataract offers an opportunity for glaucoma surgery at the same sitting.

Trabeculectomy is the most common type of surgery done for glaucoma (2). The main cause of failure of trabeculectomy is postoperative subconjunctival scarring in the filtering bleb, which is mainly mediated by fibroblast proliferation, migration and contraction. Conjunctival scarring can cause blockage of aqueous outflow by creating adhesions between conjunctiva and episclera and between scleral flap and underlying tissues.

Most of the currently used adjunctive agents that modulate wound healing are 5 Fluorouracil (5-FU) and Mitomycin C (MMC) are effective in limiting the scarring process. However they are associated with adverse effects such as hypotony, cystic thin avascular bleb, bleb leakage, bleb infection and endophthalmitis (3-5).To overcome these complications other agents to modulate wound healing have been introduced.

The Ologen collagen matrix implant is a disc-shaped porcine derived biodegradable collagen matrix that has been developed to prevent excessive scarring after trabeculectomy. It is composed of a three-dimensional porous structure of collagen & glycosaminoglycan copolymers. During trabeculectomy, the implant is placed on top of the sclera flap before the conjunctiva is closed over it. The implant regulates aqueous flow by keeping pressure on top of the sclera flap and by acting as a reservoir as aqueous humour gets absorbed into its porous structure. The collagen matrix provides a scaffold for growth of fibroblasts and guides the fibroblasts to grow through the matrix pores in a random and diffuse fashion rather than in an organised way, thus altering tissue remodelling in the trabeculectomy wound and reducing scar formation. The eventual result after resorption of the matrix would result in a loosely structured filtering bleb. Ologen has been used in trabeculectomy alone as well as in trabeculectomy combined with cataract extraction by phacoemulsification.

There are three Randomized controlled trials (RCT) comparing MMC & Ologen in trabeculectomy surgery. Two of these studies (6, 7) have shown that both MMC and Ologen are equally efficacious in controlling IOP. However the RCT by Rosentreter et al., (8) and a case control study by Boey et al., (9) showed MMC to be superior to Ologen. These studies have not addressed the use of post-operative use of 5 FU. All the RCTs have compared MMC and Ologen in trabeculectomy alone. There are no RCTs comparing the two agents in phacotrabeculectomy. There is only one interventional case control study comparing the two agents which has shown MMC to be superior to Ologen.

Different races show different response to wound healing. There is no Indian clinical trial comparing the two agents in trabeculectomy or phacotrabeculectomy. Only one published study by Tanuj dada et al., (10) was a retrospective analysis of patients undergoing trabeculectomy with Ologen and MMC. At the end of 1 year follow up IOP was lower in the combined group than controls.

Therefore more Indian studies especially Randomized controlled trials are needed to compare the efficacy of the two agents. So we conducted this RCT to compare phacotrbeculectomy with MMC versus Ologen in Indian eyes. We also looked into the requirement of additional interventions like post-operative antifibrotic agents (5 FU) and needling.

# AIMS AND OBJECTIVES

## AIM:

To compare the safety & efficacy of MMC versus Ologen in patients undergoing phacotrabeculectomy surgery.

## OBJECTIVES:

1. To compare the efficacy of MMC versus Ologen in phacotrabeculectomy.
2. To look at the bleb morphology in phacotrabulectomy with MMC versus Ologen.
3. To derermine the complications in phacotrabulectomy with MMC versus Ologen.
4. To look for differences in the requirement of additional interventions like injection 5-FU, needling and secondary surgical interventions in the two groups.
5. To compare the need for additional antiglaucoma medications required post operatively in the two groups.

# LITERATURE REVIEW

**Glaucoma** is a chronic optic neuropathy characterized by specific and progressive injury to the retinal ganglion cells resulting in damage to the optic nerve head and retinal nerve fiber layer (11)resulting in characteristic disc and field changes.

# TERMINOLOGIES

**Chronic open-angle glaucoma (COAG)**: Sheild's textbook of glaucoma (12) doesn't define POAG as a separate entity. But describes it as a COAG and defines it as a multifactorial optic neuropathy in which there is characteristic atrophy of the optic nerve. It is typically characterized by the following three criteria: (a) an intraocular pressure (IOP) consistently above 21 mm Hg in at least one eye; (b) an open, normal-appearing anterior chamber angle with no apparent ocular or systemic abnormality that might account for the elevated IOP; and (c) typical optic nerve head damage and/or glaucomatous visual field damage (12).

**Primary open-angle glaucoma (POA**G): A chronic, progressive optic neuropathy that is accompanied by a characteristic cupping and atrophy of the optic disc, visual field loss, open angles, and no obvious causative ocular or systemic conditions (13). IOP is above the 'normal range' which is defined as IOP above 2 Standard deviations from mean i.e.21 mm Hg. It is generally a bilateral disease but commonly asymmetric at presentation.

**Ocular Hypertension (OHT)**: Patients who have the first two criteria for COAG (i.e., an IOP above 21 mm Hg for which there is no apparent cause), but whose optic nerve heads and visual fields are normal are said to have ocular hypertension (12).

Individuals with IOPs of 21 mmHg (the statistical upper end of the 'normal' range) or greater, normal visual fields, normal optic discs, open angles, and absence of any ocular or systemic disorders contributing to the elevated IOPs are referred to as having ocular hypertension (13).

**Normal Tension Glaucoma (NTG)**: Open, normal-appearing anterior chamber angles with glaucomatous optic nerve head and visual field damage despite pressures that have never been documented above 21 mm Hg (12).

**Primary angle closure suspect (PAC suspect):** Greater than 270° of irido-trabecular contact plus absence of peripheral anterior synechiae (PAS) plus normal IOP, disc, and visual field (13).

**Primary angle closure (PAC):** Greater than 270° of irido-trabecular contact with either elevated IOP and/or PAS plus normal disc and visual field examinations (13).

**Primary angle-closure glaucoma (PACG):** Greater than 270° of irido-trabecular contact plus elevated IOP plus optic nerve and visual field damage (13).

## EPIDEMIOLOGY

According to the study done by WHO in 2010, there are about 39 million people blind in the whole world. India accounts for 20.5 % of all blind people in the world, second only to China which accounts for 20.9% cases. Of all the causes of blindness, glaucoma is the second most common cause after cataract. It accounts for 8% of all global causes of blindness (1).

Asians account for 47% of all cases of glaucoma and 87% of those with Angle closure glaucoma. Number of people worldwide with Open angle glaucoma and Angle closure glaucoma has been estimated to increase to 79.6 million by 2020. Out of these, 5.9 million people with Open angle glaucoma and 5.3 million people with Angle closure glaucoma will be bilaterally blind by 2020 (14).

Prevalence studies of glaucoma have been done in different parts of India which includes Vellore (15), Andhra Pradesh (16, 17), Chennai (18, 19), Madurai (20), West Bengal (21)and Chhattisgarh (22). It has been estimated that about 11.2 million in the age group of 40 years and above have glaucoma in India. Out of this 6.48 million people have POAG and 2.4 million people have PACG (23). Table 1 describes the prevalence of different types of glaucoma in these studies.

**Table 1: Glaucoma prevalence in India**

| | POAG | PACG | OHT |
|---|---|---|---|
| Vellore Eye study(15) | 0.41% | 4.32% | 3.08% |
| Andhra Pradesh Eye Disease Study(16, 17) | 2.56% | 1.08% | 0.42% |
| Chennai Glaucoma study(18, 19) | 3.51% | 0.88% | |
| Aravind Collaborative Eye study(20) | 1.7% | 0.5% | |

In the West Bengal Study (21) prevalence of glaucoma was found to be 3.4% with POAG 10 times more common than PACG. In another study done in Chattisgarh (22) prevalence of glaucoma was found to be 3.68%. Out of these POAG, PACG, Secondary glaucomas and OHT accounted for 13.1%, 21.2%, 21.2% and 14.5% of cases respectively.

# MANAGEMENT OF GLAUCOMA

The main aim of treatment is to prevent progression of functional impairment of vision within the patient's lifetime by slowing the rate of ganglion cell loss closer to that of normal population (about 5000/year). The only known modifiable risk factor for glaucoma is intra ocular pressure (IOP). It has been established by landmark Randomized Controlled Trials that reduction in IOP reduces progression in glaucoma. Early Manifest Glaucoma Trial (24) showed that by lowering the IOP by 25% the chance of progression of the disease reduced from 62% in untreated patients to 45% in the treated patients. The current mainstay of treatment of POAG and NTG is reduction of IOP.

The IOP reduction required to halt progression needs to be individualized. Generally in most patients 25- 30% reduction of IOP from the baseline is desirable. However other factors like degree of glaucomatous disc damage, visual field defects, age of the patient, and the central corneal thickness and are important parameters to be considered when determining target IOP.

**Target IOP**

The American Academy of Ophthalmology Preferred Practice Pattern Panel has defined target IOP as the upper limit of the range of measured intraocular pressures adequate to stop progressive pressure-induced injury of the optic nerve head (25). The European Glaucoma Society Panel (26) has defined target IOP as the estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage. Another definition

provided by Henry Jampel (27) is that the target IOP is the highest IOP in a given eye which does not contribute to the development of clinically apparent glaucomatous optic nerve damage. This definition takes into account the fact that glaucomatous damage of the optic nerve head is not important as long as it is not apparent in visual function tests and to the patient.

Determinants of Target IOP are:

- IOP level at which optic nerve damage occurred
- Present IOP
- Extent and rate of progression of glaucomatous damage, if known
- Presence of other risk factors
- Age of the patient
- Expected life span
- Medical history

The patient with glaucoma needs lifelong follow up. On follow up optic disc and field changes are monitored. In the event of further progression, the target IOP has to be reset at a lower level. In case of stable parameters, target IOP has to be reset at a lower level and antiglaucoma medications decreased to improve the quality of life of the patient. Different formulae have been put forward to define target IOP.

Emperical formula for target IOP by Jampel et al., (27):

Target IOP = [Initial IOP-(1-Initial IOP/100) - Z + Y±1]

Here ‘Z’ denotes the severity of optic nerve damage and ‘Y’ denotes the effect on the quality of life. The grading of these factors has been shown in table 2.

**Table 2: Jampel's formula for target IOP**

| Value | Z= Optic Nerve Damage Severity Factor | Y= Burden Of Therapy Factor |
|---|---|---|
| 0 | Normal disc and Normal visual field | No effect on QOL |
| 1 | Abnormal Disc and Normal visual field | Minimal effect on QOL |
| 2 | Visual field loss not threatening fixation | Moderate effect on QOL |
| 3 | Visual field loss threatening or involving fixation | Significant effect on QOL |

Modified from Jampel's formula (28):

Target IOP = Maximum IOP – Maximum IOP% - Z

Advanced Glaucoma Intervention Study Formula (29):

$$\text{Target Pressure} = \frac{\left(\text{1-Reference Pressure} + \text{Visual Field Score}\right)}{100} \times \text{Reference Pressure}$$

American Academy of Ophthalmology Guidelines describes target IOP as shown in table 3 (25):

**Table 3: AAO Guidelines**

| Grade | Description | Target IOP* |
|---|---|---|
| Mild | Characteristic optic nerve abnormalities are consistent with glaucoma, but the visual field is normal | 20% |
| Moderate | Visual field abnormalities exist in one hemifield and are not within 5° of fixation and Normal Tension Glaucoma | 30% |
| Severe | Visual field abnormalities exist in both hemifields, or visual field loss is within 5° of fixation | 40% |

*(% Reduction from Baseline)

The various approaches to achieve this goal include medical therapy, laser trabeculoplasty, filtering surgery, and cyclodestructive procedures, each of which has its own risks and benefits.

**Medical therapy**

Medical therapy involves administration of antiglaucoma medications to the patient to achieve the target IOP. Topical medications (eye drops) include:

1. β adrenergic antagonists
2. Prostaglandin analogues
3. Carbonic anhydrase inhibitors
4. Adrenergic agonists
5. Parasympathomimetic agents

The role of systemic carbonic anhydrase inhibitors and osmotic agents like glycerol and mannitol is limited and temporary in open angle glaucoma. It is used in patients with high uncontrolled IOP despite topical medications, awaiting surgery to stabilize the IOP prior to surgery. However these agents are very essential in the intial management of acute angle closure glaucoma. The role of neuroprotective agents is not yet established.

Antiglaucoma medications are ideally started in one eye and one agent at a time - uniocular therapeutic trial- in order to establish the efficacy of the drug. Depending on the severity of glaucoma and the socioeconomic status of the patient, β blockers or Prostaglandin analogues form the first line drugs of choice. Further additional medications and combination therapies with two or usually not more than three classes of drugs may be added as per the individual patient's target IOP.

Compliance, affordability, side effects and effect on the quality of life of the patient are to be kept in mind before selecting the drug for the individual.

**Laser therapy**

The second modality of treatment is laser therapy. Different types of laser surgery are as follows:

1. Laser peripheral iridotomy: It is done to prevent or treat pupillary block in angle closure. The role of laser PI in open angle glaucoma is limited to pigmentary glaucoma in its active phase.

2. Laser iridoplasty or gonioplasty: It is indicated in patients with plateau iris syndrome to contract the peripheral iris and hence pull it away from the angle.

3. Laser trabeculoplasty: ALT is the most commonly performed procedure. It can be of different types like argon laser or selective laser or diode laser trabeculoplasty. It is a treatment option in a patient with open angle glaucoma when maximum tolerated medical therapy is not able to achieve the target IOP. Advanced Glaucoma Intervention study was a RCT comparing two treatment sequence: Argon laser trabeculoplasty- trabeculectomy- trabeculectomy (ATT) and Trabeculectomy- Argon laser trabeculoplasty- trabeculectomy (TAT). They concluded that ATT sequence was beneficial for black race and the TAT sequence for the white race (30). However a later report didn't support this view (31). It may also be used as a primary treatment for glaucoma and in patients who are non compliant and systemically unfit to undergo surgeries. It is especially effective in POAG, pigmentary glaucoma and PEX glaucoma. However the IOP reduction achieved by laser is not long lasting as shown by various studies.155-162(32-39). 19% - 23% cases fail in the first year followed by a failure rate of 5% - 9% per year.160-162 (37-39). At the end of 5 and 10 years, half and two third of the patients fail (39).

4. Excimer laser trabeculostomy: It involves making a communication between the juxtacanalicular trabecular meshwork and the Schlemm's canal which are the major site of obstruction in open angle glaucoma. Study by Neuhann et al., (40) demonstrated a 40% decrease in IOP at 6 months follow up in 14 eyes.

5. Cyclophotocoagulation: It involves destruction of the epithelium, stroma and vasculature of the ciliary body and hence decreasing the aqueous humour production. It is generally used in symptomatic (pain) patients with advanced glaucoma with very poor visual prognosis. It is rarely tried as the last resort when all other modalities of treatment fail or patients are systemically unfit to undergo glaucoma surgical procedures.

**Surgical treatment**

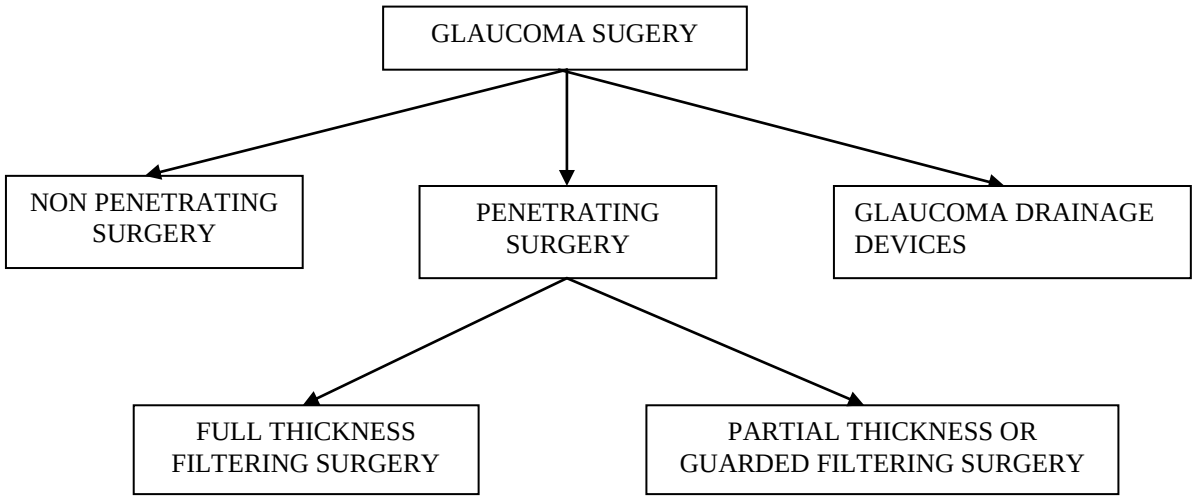
The third and one of the most important modality of treatment is surgical treatment. Indications of surgery:

1. Patients noncompliant with medical management.
2. Patient not affording antiglaucoma medications.
3. Patients non tolerant to the side effects of the antiglaucoma medications.
4. Uncontrolled IOP and progression of optic disc and field changes despite maximum tolerated medical therapy and laser therapy.
5. Advanced glaucomatous field defect threatening central vision.
6. Combined with cataract surgery if IOP is borderline high or there is advanced glaucomatous field and disc changes.

Collaborative Initial Glaucoma Treatment Study showed that surgical therapy achieves better IOP control than medical therapy but visual field progression was similar in the two groups (41).

Surgical therapy is more likely to keep IOP at a lower level for longer period of time (42-46). In comparison to medications, surgery is likely to ensure stable low IOP throughout the day thus reducing the diurnal variation of IOP and hence progression of glaucoma despite treatment. Hence surgery may be indicated in those patients with progression of glaucoma despite documentation of adequate reduction in IOP on medications. Quality of life may be better in the surgical group on the long run. While quality of life may be affected adversely due to side effects of the antiglaucoma medications. Surgery is less dependent on the compliance of the patient. Cost of the surgery, if not associated with complications may be less than the life time need for multiple antiglaucoma medications.

The flowchart below explains the different types of glaucoma surgery.




In penetrating glaucoma surgeries a fistula is created into the anterior chamber so that aqueous flows out to the subconjuctival space forming a bleb. Full thickness filtering surgeries were the first type of glaucoma surgery introduced. They are obsolete now. In these surgeries the fistula connecting the sub conjunctival space to the anterior chamber is covered only by the conjunctiva and tenon's capsule. They are therefore associated with more chances

of hypotony, shallow anterior chamber, premature cataract and bleb failure. They include following types of surgery:

1. Sclerectomy
2. Thermal sclerostomy
3. Trephination
4. Iridencleisis

Sclerectomy involves creating a limbal fistula with different techniques. Anterior lip sclerectomy was first introduced by LaGrange in 1906 (47). In this surgery a full thickness limbal fistula was made and then a piece of tissue was excised from the anterior aspect of the wound. 3 years later it was modified by Holth (48) when he used a punch to create the sclerectomy. Iliff and Hass (49) further introduced the technique of posterior sclerectomy which became popular in mid $20^{th}$ century.

Thermal sclerostomy was first described by Preziosi in 1924 (50). In this surgery an electrocautery was used to make the limbal fistula. It was later modified by Scheie (51) in which limbal incision was first marked with a scratch and then the cautery was applied.

In 1909 Elliot (52) and Fergus (53) introduced the technique of trephination at the corneolimbal junction. Elliot (54) further modified it by doing trepination more anteriorly at the sclerocorneal junction. However it was associated with the formation of thin blebs with increased chances of infection. Therefore Sugar (55) modified it to limboscleral trephination in which the trephination was done more posteriorly.

In iridencleisis, iris tissue was incarcerated in the limbal incision and it was supposed to act as a wick and facilitate aqueous outflow. However it is now an obsolete surgery because of the increased chances of sympathetic ophthalmitis.

In non penetrating surgeries anterior chamber is not entered and the trabecular meshwork is left intact. This reduces the chances of hypotony, overfilteration and the consequent sequale. Two lamellar sclera flaps are made and the deeper flap is excised.

The first non penetrating surgery known as sinusotomy was first introduced by Krasnov (56). In this surgery Schlemm's canal is exposed after excision of a small strip of sclera. In another type of non penetrating surgery known as nonpenetrating trabeculectomy deep dissection is done to the level of Schlemm's canal to expose the trabecular meshwork but leaving it intact (57).

At present there are mainly two types of non penetrating surgery performed:

1. Deep sclerectomy
2. Viscocanalostomy

In the former a Descemet's window is created through which aqueous humour flows into the subconjunctival space forming a bleb. A modification is placement of a collagen implant in the scleral bed which increases the success rate of the surgery (58-60). In the latter surgery a filtering window is created and then a viscoelastic agent is used to dilate the Schlemm's canal which is supposed to create microruptures in the trabecular meshwork. However these surgeries are technically more demanding and require meticulous dissection without entering the trabecular meshwork.

Trabeculectomy is the prototype of the guarded filtering surgery performed routinely by most glaucoma surgeons worldwide (2). The concept of trabeculectomy was first put forward by Sugar in 1961 (61)and popularised by Cairns in 1968 (62).The basic mechanism of surgery is to create a fistula at the limbus which allows the aqueous humour to flow out, past the angle of anterior chamber, where the basic pathology lies. This fistula is covered with a partial thickness sclera flap to control the aqueous outflow and consequent hypotony. The outflowing aqueous accumulates under the conjunctiva forming a filtering bleb. Amount of flow depends on the tightness and thickness of the sclera flap as well as the overlap between the trabeculectomy site and the sclera flap. Most/Some studies have shown penetrating glaucoma surgeries to be superior to nonpenetrating surgeries in lowering IOP (63-65).

Glaucoma drainage devices are the surgery of choice after failed filtering surgery with antifibrotic agents in adults as well as in congenital glaucoma. They are the primary surgical choice in conditions where primary trabeculectomy is likely to fail like neovascular glaucoma (NVG), uveitic glaucoma and angle recession glaucoma. They can be either valved or non valved implants. Baerveldt implant and Molteno implant are the examples of the former while Ahmed glaucoma valve and Krupin implant are examples of the latter.

## COMBINED CATARACT AND GLAUCOMA SURGERY

In a patient with both cataract and glaucoma, the type of surgery has been a matter of controversy. Sequential cataract and glaucoma surgery and combined surgery are the two options. Two important developments have contributed to the increased rate of combined surgery as compared to sequential cataract and glaucoma surgery. The first of these is the

evolution of phacoemulsification surgery with foldable intra-ocular lenses. Decreased wound size, decreased postoperative inflammation and different choices for surgical entry sites have led to early post-operative rehabilitation and good visual outcome. The second is the introduction of antifibrotic agents in glaucoma surgeries which enhance the success rate.
Secondary phacoemulsification with IOL implantation surgery has adverse effects on the pre-existing filteration bleb.Studies have shown that cataract surgery after a glaucoma surgery can lead to bleb failure in 30-40% cases (66-68). It increases post-operative IOP, alters the bleb morphology and increases the need for anti glaucoma medications (69-72).

Studies have shown IOP spike in two third patients undergoing cataract surgery with pre existing glaucoma as compared to 10% in controls (73). One study demonstrated 2.5 times increase in IOP after cataract surgery alone than combined surgery (74).

Phacoemulsification with IOL implantation combined with trabeculectomy is associated with significant lowering of IOP and number of antiglaucoma medications (75).

Studies have proven that phacoemulsification with IOL implantation combined with trabeculectomy is superior to extracapsular catarct extraction (ECCE) with IOL combined with trabeculectomy. The former resulted in lower IOP, lesser complications and better bleb morphology (76-80).

There are two options for combined phacoemulsification and trabeculectomy surgery. It can either be a single site or double site surgery depending on the site for trabeculectomy and corneal entry wound. Various studies have shown that both the surgical approaches are equally effective in lowering IOP (81-87).

## ANTIFIBROTICS

Glaucoma surgery is unique in the fact that incomplete wound healing is a desirable outcome. A completely healed filtering bleb results in failure. Wound healing process involves mainly two procedures: replacement and regeneration. The former involves formation of scar tissue to replace the original tissue while the latter means regeneration of the original tissue without any signs of the insult.

Wound healing can be divided into four different phases:

1. Clot phase
2. Proliferative phase
3. Granulation phase
4. Collagen phase

After any injury like surgical trauma a cascade of events is started which includes inflammation and clotting, which results in release of multiple cellular, hormonal and growth factors. These factors lead to migration of neutophils, monocytes, macrophages and fibroblasts. Fibroblasts produce collagen, elastin and mucopolysaccarides, which lead to formation of scar tissue.

The most common cause of failure of filtering surgery is scarring of the bleb. This scarring can occur either between the conjunctiva and episclera or between the sclera flap and the underlying tissues. It is caused by proliferation, migration and contraction of the fibroblasts.

This wound healing response can be altered by interfering at any one of the steps described above.

Various adjunctive agents have been described to improve the success rate of the glaucoma surgery. The most important among these agents are corticosteroids, 5-FU and MMC.

Corticosteroids act as anti-inflammatory and immunomodulatory agents. They inhibit release of inflammatory mediators, growth factors and prevent phagocytosis. This eventually decreases the fibroblastic activity and hence wound healing. The use of topical steroids in the post operative period is justified but studies have shown that systemic steroids do not have any additional advantage (88, 89).

5-FU and MMC were introduced as adjunctive agents in trabeculectomy to enhance the rate of surgical success (90-93). However their use is associated with more post-operative complications including sight threatening consequences like bleb leak, hypotonic maculopathy and endophthalmitis (3-5).

5-FU is a chemotherapeutic agent which undergoes metaoblic transformation and binds to thymidylate synthetase. It is a pyrimidine analogue and an antimetabolite. It inhibits DNA synthesis and causes cell death. It can also get incorporated into m RNA and hence inhibit protein synthesis.It can either be used intraoperatively or in postoperative period. Intraoperatively sponges soaked in 25-50 mg/ml of 5- FU is applied at the surgical site for 5 minutes (94-98).

Post operatively 5FU can be used as subconjunctival injections .Some studies have advocated daily administration of 5 mg of 5-FU from 7 to 14 days (99-101).Few recommend its use from first postoperative day. Success has been reported with its use from 3 to 15 days whenever signs of impending bleb failure are noticed (102, 103). Various studies have been done to evaluate the intra-operative and postoperative use if injection 5-FU. These are shown in table 4 and 5 below.

**Table 4: Summary of studies using postoperative 5-FU**

| **Authors** | **Study design** | **Number of eyes** | **Dose** | **Outcome (study versus controls)** |
|---|---|---|---|---|
| Heuer et al., (104) | Pilot study, complicated glaucomas, historical controls | 104 | 3 mg or 5 mg injections, 105 mg over 2 weeks | 69% vs 39% |
| FFSS group., (105) | Prospective, randomized study, in patients with history of cataract surgery or failed filter | 213 | 5 mg injections, 105 mg over 2 weeks | 49% vs 26% |
| Araie et al., (106) | Prospective, non-randomized mixed, POAG, secondary and refractory glaucoma | 362 | Mean dose, 36.8 mg in POAG group, 49.5 mg in secondary glaucoma, 36.5 mg in refractory group | IOP < 16 mm Hg 55.2% vs 0% |
| Goldenfeld et al., (107) | Prospective, randomized study in primary trabeculectomy | 62 | 5 mg injections, 5 injections between day 1 and day 15 | IOP < 20 mm Hg in 94% vs 73% |
| Ophir et al., (108) | Prospective, randomized study in primary trabeculectomy | 41 | 4–6 5 mg injections | IOP < 20 mm Hg in 96% vs 76% |
| Ren et al., (109) | Prospective, randomized study in patients undergoing combined phacotrabeculectomy | 74 | 5 mg injections over first 2 postoperative weeks | No difference in two groups |

**Table 5: Summary of studies using intraoperative 5-FU with or without postoperative 5-FU**

| Authors | Study design(no. of eyes) | Dose (application for 5 minutes) | Post op 5FU | Outcome |
|---|---|---|---|---|
| Dietze et al.,(110) | Consecutive case series (20) | 50 mg/cc sponge | No | 84% had IOP < 21 reduction of at least 20% at 3 months |
| Anand et al.,(111) | Prospective, non-randomized study (76) | 25 mg/cc sponge | No | 84% had IOP < 21 reduction of atleast 20% at 3 months |
| Mora et al.,(112) | Restrospective study (140) | 50 mg/cc sponge | Yes | Mean IOP in high-risk patients not receiving post-op 5-FU was 15.3mmHg<br>Mean IOP in low-risk eyes receiving post-op 5-FU was 10.8 mm Hg |
| Towler et al., (113) | Restrospective study (50) | 25 mg/cc sponge | Yes | IOP < 20 mm Hg in 82% at 1 and 2 years and 67% at 5 years |

Experimental studies in rabbits have shown that 5-FU decreases the mitosis and differentiation of corneal epithelium as compared to controls. (114)

5-FU is toxic to actively replicating cells like corneal epithelium. It presents as punctate keratopathy, filamentry keratopathy, epithelial defects, whorl like or striate melanokeratosis. It can lead to secondary complications like corneal ulceration, corneal melt and perforation. It is also associated with complications like conjunctival wound leaks in early postoperative period and late onset bleb leakage (115-116).

MMC is an antibiotic derived from fungus - *Streptomyces caespitosus*. It is a cell cycle non specific alkylating agent which cross links DNA and thus inhibits DNA replication, mitosis

and protein synthesis. Its use as an adjunct to lower IOP in trabeculectomy was first described by Chen in 1983 (117).

MMC has shown to decrease the proliferation of fibroblasts in tissue culture studies of tenons capsule fibroblasts and this correlates with the outcome of filtering surgery[72-73].(118-119) MMC has shown to enhance the success of trabeculectomy in uveitic glaucoma, congenital and developmental glaucoma, normal tension glaucoma, refractory glaucoma in black patients and primary uncomplicated trabeculectomy (120-126).

Since the outcome of combined cataract and glaucoma surgery may not be as favourable as glaucoma surgery alone, the use of antifibrotics is justified in combined surgery (127). MMC has been demonstrated to have additional advantage in combined surgery by lowering IOP, eliminating the need for additional antiglaucoma medications and formation of larger filtering blebs (128-129). Various studies have been done to evaluate the efficacy of these agents. This is shown in table 6 below.

**Table 6: Summary of studies comparing intraoperative MMC versus 5-FU in combined procedures**

| **Authors** | **No. of eyes** | **Study Design** | **Outcome** |
|---|---|---|---|
| Cohen et al., (130) | 72 | Prospective, double masked, placebo controlled | IOP lower at all time points, more early bleb leaks in MMC |
| Budenz et al., (131) | 78 | Retrospective | IOP significantly lower from preop in all groups, MMC group < than 5FU but not lower than no antifibrotic |
| Carlson et al., (132) | 29 | Prospective, randomized placebo controlled | 3.0 mm Hg greater mean IOP reduction in MMC group |
| Shin et al., (133) | 197 | Prospective, randomized placebo controlled | No overall difference |

MMC is more potent than 5-FU and hence may also have prolonged cytological toxicity. Experiments on cultured mouse fibroblasts and bovine vascular endothelial cells have shown that 5-FU is toxic only to the former while MMC is toxic to both the cell types (134-135).

MMC can lead to formation of thin walled avascular blebs and late onset bleb leaks. This is three times more common with MMC than 5-FU (136). This may ultimately result in endophthalmitis. Such avascular thin blebs lead to overfiltration and subsequent hypotony. The consequences of hypotony include choroidal detachment, shallow anterior chamber, corneal decompensation. The term hypotonic maculopathy was coined by Gass in 1972. The entity includes disc edema, vascular tortuosity and macular chorioretinal folds leading to decrease in visual acuity. He proposed that it was caused due to contraction of the elastic sclera leading to chorioretinal folds (137).

The mechanism for hypotony is overfilteration which has been supported by histological studies of excised blebs which showed irregular epithelium and acellular subepithelium of loose connective tissue (138-140). Another proposed mechanism is aqueous hyposecretion. Enucleated human eye showed disruption of ciliary body epithelium at the site of application of MMC. Monkey and rabbit eyes showed suppression of aqueous flow (141-143). Early postoperative hypotony can later lead to failure of the bleb. Hypotony results in formation of secondary aqueous which contains factors which increases wound healing and hence scarring around the sclerostomy site (144).

Zacharia et al in a retrospective study found incidence of hypotony of 1 in 3(defined as IOP < 5mm Hg). 0.4 mg MMC was used for duration of 3.5 to 7 minutes in 52 eyes of 48 patients.7

eyes required surgical intervention for hypotony. They also found that longer time of application increased the chances of hypotony (145).

In a case series of 10 patients MMC was used after pterygium surgery. It was associated with side effects like scleral and corneal melt, corneal edema, scleral calcification, iritis, corectopia (146). MMC is also associated with endothelial toxicity. A study demonstrated that MMC caused 10-11% more loss of endothelium as compared to controls (147).

Different studies have demonstrated that MMC use is associated with higher rate of endophthlamitis (148-152). Greenfeld et al., (148) did a retrospective analysis and followed 609 eyes and followed them for 3 months. Bleb associated endophthalmitis developed in 2.1% patients and the most common organisms isolated were S*treptococcus sanguis* and *Haemophilus influenza.* The rate of endophthalmitis was 13% and 1.6% for the inferior and superior blebs respectively. However it also included inferior trabeculectomy.

A retrospective study by Peter de et al (150) was done on 239 eyes of patients undergoing trabeculectomy with MMC with a follow up of 7 years.0.5 mg/ml MMC was used for 30 seconds to 5 minutes in different patients. The complications of bleb leak, blebitis and endophthalmitis were seen in 20 eyes (8%), 5 eyes (2%) and 8 eyes (3%) respectively.5 year probability of bleb leak, blebitis and endophthalmitis was calculated to be 17.9%, 6.3%, 7.5% respectively by Kaplan meier analysis.

Another retrospective case series by Rajiv Bindish et al., (153) was done on 123 eyes of patients undergoing primary trabeculectomy with MMC with a follow up of 4 years. Weck-cell soaked sponge of MMC 0.25, 0.33, 0.5 mg/ml was used for 0.5 to 5 minutes duration.

The complications of hypotony, hypotonic maculopathy, bleb leak, blebitis, endophthalmitis was seen 42.2%, 8.9 %, 14.6%, 5.7 %, 0.8% of eyes respectively. These complications were seen at a mean follow up of 26.1 months, 33.7 months, 27.9 months, 35.4 months, 15 months respectively.

A retrospective analysis of 632 patients was done by Kiyofumi et al., (154) trabeculectomies were performed with or without MMC or 5FU. At a mean follow up of 3.5 years, bleb related infection was seen in 1.3%, 1.3%, 1.1 % of cases without any antifibrotic agent, with 5-FU and with MMC respectively. All the cases that developed infection were associated with avascular or hypovascular cystic blebs and low IOP. There was no difference in the incidence of bleb related infection in the three groups[110].

A retrospective analysis[111] of 609 eyes was done by David et al., (155). These patients underwent trabeculectomies in conjunction with MMC. Average follow up was 16.0+/-11.5 months. 13 eyes developed endophthalmitis (2.1%). It was more common with inferior trabeculectomies than superior trabeculectomies (7.8% per patient-year vs 1.3% per patient-year). Cumulative incidence was 13% and 1.6% respectively for inferior and superior blebs. The rate of endophthlamitis in trabeculectomies without antifibrotics has been reported to be 0.2-1.5%.

A retrospective analysis was done by Takashi et al., (156). The study included 123 eyes which underwent trabeculectomy with MMC. 0.4 mg/ml MMC was used for 3 minutes. At the end of 8 years follow up bleb leak, hypotonic maculopathy, bleb related infection was seen in 7.9 %, 8.3 %, 5.9 % cases respectively.

Different protocols for MMC application have been described but there is no optimum protocol established. In early protocols 0.5mg/ml of MMC was applied for 5 minutes. Some retrospective studies advocate application of .02% MMC for 2 minutes (157). It is adviced to assess each patient and the associated risk factors individually and hence determine the dosage accordingly. Table 7 describes various studies comparing MMC and 5-FU in trabeculectomy.

**Table 7: Summary of the studies comparing MMC and 5-FU in trabeculectomy**

| **Author** | **No. of eyes** | **Dose** | **Follow up in months** | **Outcome ( MMC versus 5FU)** |
|---|---|---|---|---|
| Lamping and Belkin (158) | 80 | Adjunctive MMC versus 5 FU | 12 | Mean IOP: 12.8 vs 14.8 (p=0.001) |
| Smith et al., (159) | 73 | MMC 0.2 mg/ml for 3–5 minutes or 5-FU 50 mg/ml for 5 minutes | 20.9 | Mean IOP: 10.2vs 9.7 (p<0.001) |
| Singh et al., (160) | 108 | MMC 0.4 mg/cc for 2 minutes with 5-FU 50 mg/cc for 5 minutes | 10-11 | No difference |

Other antifibrotics which have been evaluated includes cytosine arabinoside, bleomycin, rapamycin, doxorubicin, daunorubicin, 5-fluoroorotate, heparin, taxol, cytochalasin-B, colchicine, immunotoxins, Suramin and interferon α2b.

Suramin is a growth factor inhibitor. It's efficacy has been studied in rabbits (161) and humans (162). In a prospective study (162) Suramin was found to have success rates comparable to MMC and complications less than MMC.

β irradiation can delay healing of wound which has been demonstrated in rabbit studies (163). Also tissue culture experiments have shown inhibition of fibroblast growth by β irradiation.

Study by Miller et al., (164) in patients with congenital glaucoma demonstrated beneficial effect of β irradiation on trabeculectomy.

Other alternatives of MMC tried are amniotic membrane transplant (165) and subconjuntival perfluoropropane (166-167).

Agents which alter other phases of the wound healing have also been evaluated. For example, tissue plasminogen activator, which causes localized fibrinolysis, ¥interferon and calcium ionophores, which inhibit collagen biosynthesis and D-penicillamine, which inhibit cross-linking of collagen, have shown promise in in vitro and in vivo studies (168-169).

Various biodegradable implants have been tried in glaucoma surgeries. A polyfilm (L lactideco- epsilon-caprolactone) has been shown to be superior to controls in lowering IOP and equally efficacious to MMC in rabbit eyes (170). It is a 7µm thick implant which has two surfaces. The surface with a honeycomb pattern is placed facing the tenon's capsule and the other surface which is smooth faces towards the sclera. The honeycombed surface acts as a barrier for formation of fibrous scar tissue and inhibits inflammation.

Two other implants: seprafilm (sodium hyaluronate and carboxymethylcellulose) and hyaluronic acid–carboxymethyl cellulose film have been shown to reduce postoperative scarring in glaucoma surgeries (171-172). In a study by Tsurumaru et al., (171) in rabbits IOP was significantly lower in cases than controls (p= .0044) at 28 days follow up. Histological analysis showed lesser adhesions between the sclera and the conjunctiva in the cases than the controls (p=0.0041).

## OLOGEN

Ologen (Aeon Astron Europe BV, Leiden, the Netherlands) is a porcine derived biodegradable implant. It is a three dimensional polymer made up of lyophilized collagen (>90%) and glycosaminoglycan (<10%). It causes wound healing by a non scarring process without using anti-fibrotic agents. It induces the conjunctival fibroblasts and myofibroblasts to grow randomly within its porous structure and secrete a loose connective tissue matrix. It thus creates a new physiologic environment in the filtering bleb reducing wound contraction. It acts like a reservoir, a buffering system and maintains a controlled drainage of aqueous. It induces a regenerative non scarring process of wound healing. It is the first application of bioengineering to glaucoma. Animal studies have shown it to be effective in glaucoma filtering surgery (173-174).

The pore diameter varies from 10-300 um. There are various models depending on the dimensions of the implant as shown in table 8 below.

**Table 8: Dimensions of the different models of Ologen**

| Model | Height (mm) | Diameter (mm) |
|---|---|---|
| 830601 | 2.0 | 6.0 |
| 830661 | 4.0 | 7.0 |
| 830681 | 4.5 | 7.5 |
| 830691 | 5.0 | 10 |
| 862051 | 1.0 | 12.0 |

There is a newer version of Ologen implant, named as version 2. It is made up of atelocollagen. Structure of the collagen molecule consists of aminoacid sequence known as

telopeptide at the C and N terminal. It confers immunogenicity to the collagen molecule. Atellocollagen is obtained by treatment with pepsin and is free of telopeptides. Therefore it has lower immunogenicity. It is said to have additional anti-inflammatory action in the surrounding tissue (173).

Non ophthalmological uses of atelocollagen include intradermal injection in plastic surgery, as a substitute of bone cartilage, wound healing**.** This version has been used in our study-830601 with dimensions of 2 x 6 mm.

The implantation is a simple procedure and requires minimal modification during the surgery. It is placed over the sclera flap before closing the conjunctiva and tenon's capsule in a water tight fashion. Animal studies have shown that the implant completely degrades in 30-60 days (174).

It does not cause complications associated with antifibrotic agents like ocular surface toxicity, endothelial toxicity, wound leak, hypotony, hypotonic maculopathy, blebitis, endophthalmitis. Also MMC is teratogenic, increases the operating time and has specific disposal requirements. Ologen does not have any such disadvantages. It applies a dynamic pressure over the sclera flap and hence maintains a dynamic fluid control and prevents hypotony. However the cost is Rupees 4,700 which limits its routine use in developing countries like ours.

Indications for use of Ologen:

1. Failed Trabeculectomy

2. Primary Trabeculectomy (combined and sequential )

3. Pterygium Surgery
4. Strabismus surgery
5. Ocular surface reconstruction
6. Sub conjunctival scar revision

## STUDIES COMPARING MMC AND OLOGEN IMPLANT

Since the introduction of Ologen implant, various studies have been done to evaluate its efficacy in different types of glaucoma surgeries. There are four studies comparing Ologen with MMC. There are three Randomized Controlled Trials (RCTs) comparing MMC and Ologen implant in trabeculectomy. One study by Boey et al (9) studies compared the two agents in phacotrabeculectomy surgery. Table 9 summarizes these studies:

**Table 9: Summary of studies comparing MMC versus Ologen**

| Author | Study type | Follow up period | Total no. of patients | Type of surgery | Ologen model | MMC | Results | P value |
|---|---|---|---|---|---|---|---|---|
| Marey et al., (6) | RCT | 1 year | 60 (30 in each) | Trabeculectomy | 830601 | 0.2mg/ml for 2 min | MMC and Ologen equally efficacious | 0.581 |
| Boey et al., (9) | Prospective interventional case control study | 3 months | 66 (33 in each) | Phaco trabeculectomy | 83068 | 0.4 mg/ml for 2 min | IOP control better in MMC than Ologen | <0.001 |
| Rosentreter et al., (8) | RCT | 1 year | 20 (10 in each) | Trabeculectomy | Version1 (model no. not mentioned) | 0.2 mg/ml for 3 min | IOP control better in MMC than Ologen | 0.01 |
| Cillino et al., (7) | RCT | 2 years | 40 ( 20 in each) | Trabeculectomy | 830601 | 0.2mg/ml for 2 min | MMC and Ologen equally efficacious | 0.92 |

RCT done by Marey et l., (6)included 60 patients with the diagnosis of POAG, CACG, PEX Glaucoma, uveitic glaucoma and pseuodphakic glaucoma. They used 0.2mg/ml MMC for 2 minutes and Ologen model 830601. Absolute success was defined as IOP < 21 mm Hg without any topical medications. At the end of 1 year there was no significant difference in IOP (p value=0.581) and complication rate (p value=0.678) in between the two groups. Bleb morphology was studied using Moorfields bleb grading system. No statistically significant difference was seen in the bleb area and height score. Bleb vascularity score was higher in the MMC group (p value= 0.001).

A prospective interventional case control study was done by Boey et al., (9) to compare phacotrabeculectomy with ologen implant versus MMC. It included 33 patients diagnosed to have POAG and PACG in each group. Patients underwent two site phacotrabeculectomy. In the MMC subgroup 0.4 mg/ml MMC was applied for 2 minutes duration. Patients were followed for a period of 3 months. Mean reduction of IOP was greater in the MMC group (p value < 0.001). Bleb morphology was evaluated using Moorfields bleb grading system at the end of 60 days. Bleb vascularity score was higher and bleb height, lower in the ologen group. The bleb height in ologen group was mainly because of the implant while in the MMC group it was due to the aqueous lake in the bleb. Anterior Segment OCT showed retained ologen implant in 39.4 % cases at the end of 3 month follow up.

RCT was done in Germany by Rosentreter et al., (8). It compared Ologen and MMC in trabeculectomy. It was done in patients diagnosed with open angle glaucoma with a follow up of 1 year. 20 patients were randomized to either MMC or Ologen group. In the former group

0.2mg/ml MMC was applied for 3 minutes after making a fornix based conjunctival flap. In the latter group version 1 of Ologen implant was placed over the sclera flap before closing the conjunctiva. One difference in the suturing technique in Ologen group was that a loose scleral flap suture was placed in place of tight suture in MMC group. Complete success was defined as IOP </= 18 mmHg or 20 % reduction in IOP without any antigaucoma medications or any additional surgery. After 1 month of follow up onwards significant IOP difference was seen in both the groups, with IOP being lower in the MMC group. Complete success was achieved in 100 % patients in MMC group while only 50% patients achieved complete success in the ologen group (p value =0.01). No significant difference was seen in the rate of complications in both the groups. Early hypotony was common in the ologen group which may be attributed to loose suturing of the sclera flap in this group. Morphology of the bleb was studied using Wuzberg Classification system. In the MMC group blebs were more prominent, more avascular with more microcysts, while in the ologen group blebs were more flat, diffuse and vascular. One patient in mitomycin group developed vascular bleb with leak at 3 month follow up and required revision surgery. Ologen implant was not visualized in any patient by ultrasouind biomicroscopy at the end of 1 month.

Another RCT was done in Italy by Cillino et al., (7). It included 40 patients of POAG/PEX Glaucoma and they were followed for a period of 24 months. MMC was used at a concentration of 0.2 mg/ml and applied for duration of 2 minutes. As in the above mentioned study ologen implant was placed over the sclera flap after suturing it with a loose suture. Target IOP was divided into three subgroups: </=21 mm Hg, </=17 mm Hg and </=15 mm Hg. Complete success was defined as achieving the target IOP without any medications or additional surgery. There was no significant difference in the success rate between the two groups (p value=1.0; 1.0; 0.75 in each target group respectively). Also there was no

statistically significant difference in the complication rates between the two groups. Bleb evaluation was done using Moorfields Bleb Grading System and Spectral domain OCT. Bleb height was higher in the ologen group as compared to the MMC group. But there was no difference in the bleb area and vascularity score between the two groups.

A randomized clinical trial[125] was done by Dimitris et al., (175) in Greece. It compared trabeculectomy with and without Ologen implant. 40 patients were randomized and followed for 6 months period. There was no additional benefit seen in patients who underwent trabeculectomy with Ologen implant (p value=0.985). Though there was no statistically significant difference between the two groups in complications, one patient developed endophthlamitis and two other patients developed shallow anterior chamber secondary to leak and required resuturing in the Ologen group.

Version 2 of Ologen implant was used in a study done by Rosentreter et al., (176); evaluating its efficacy in revision surgery after failed glaucoma drainage surgery. It was an observational comparative case series. 10 patients underwent revision surgery with Ologen implant and MMC while 9 patients were retrospectively observed who underwent capsule excision with MMC alone. The success rate was significantly better in the Ologen group (p value=0.04).
Aptel et al., (177) studied the efficacy of Ologen implant in deep sclerectomy surgery. It was a case series of 15 patients with POAG There was a significant reduction of IOP (p value= <.001) at the end of three month follow up visit.

There are no randomized controlled studies in Indian eyes comparing MMC and Ologen in either trabeculectomy or phacotrabeculectomy. There is only one study by Tanuj Dada et al., (10) done in Dr. Rajendra Prasad Eye Institute, New Delhi. It was a retrospective study which

included 33 eyes of 24 patients who underwent trabeculectomy with Ologen and MMC-0.1mg/ml for duration of 1 minute. At the end of 12 months follow up period IOP was significantly lower in the Ologen with MMC group than the control (p value < 0.001).
Different races respond differently to wound healing after any glaucoma surgery. So we need more Indian studies to evaluate the efficacy of Ologen implant.

Out of the 3 randomized control trial comparing MMC and Ologen, the study done by Rosentreter et al., (8)demonstrated MMC to be superior to Ologen implant whereas study by Cillino et l., (7) and Marey et al., (6)showed Ologen to be as efficacious as MMC in control of IOP. The case control study by Boey et al., (9) in phacotrabeculectomy also showed MMC to be superior to Ologen. Also the randomized control trial comparing Ologen to placebo by Dimitris et al., (175) showed no benefit of Ologen implant over trabeculectomy without implant. Version 2 of Ologen implant was used by Cillino et al., (7), Marey et al., (6)and Rosentereter et al., (8). The observational comparative case series by Rosentreter et al., (8) evaluated efficacy of Ologen and MMC versus MMC alone in the revision surgery done after failed glaucoma drainage device surgery. This study demonstrated the former to be better than the latter. More studies, specially randomized controlled trials are needed to evaluate its efficacy.

None of these studies have studied the role of post operative use of 5-FU along with Ologen. Postoperatively in vascular blebs, subconjunctival 5-FU injections can help decrease the vascularity and improve the success rate of trabeculectomy surgery.

Therefore a randomized control study is required which can compare MMC and Ologen implant (version 2) in Indian eyes in conjunction with post-operative 5-FU.

**BLEB GRADING SYSTEMS**

Morphology of bleb is an indicator of bleb function and can predict long term success and bleb related complications (178-180). There are various classification systems for bleb morphology.

**Moorfield's bleb grading system** (181) is one of them which assess bleb area, height and vascularity**.** It is a system of grading in which photographs of the bleb area is compared to a standard photograph. Photograph is taken with eye looking down with maximum part of superior conjunctiva visible. The canthal margins are the horizontal limits of the photograph. Grading is then done with the photographs magnified to a diagonal length of 15 inches. They are compared to a standard set of photographs. Bleb is graded to the best possible match out of the set of standard photographs as shown in Appendix G.

Three aspects are evaluated- bleb area, height and vascularity. There are six criteria to be assessed- 2 describing area, 1 for height and 3 for vascularity.

1. Area: It is divided into a central demarcated area and peripheral margins. It is graded in relation to the total superior conjunctiva visible.

1a. It is the bleb area above the sclera trap door. If not visible then it is graded same as the peripheral area. It is graded depending on the extension.

1= 0 %
2= 25 %
3= 50 %
4= 75 %

5= 100 %

2a. It is the total area of the bleb in comparison to the total superior conjunctiva visible. It is similarly graded depending on the extension:

1= 0 %
2= 25 %
3= 50 %
4= 75 %
5= 100 %

2. Height: Score is given after comparing it to a standard reference photograph. It is given a score of 1-4 with increasing height. This is applied to the highest point on the bleb, usually at its centre.

3. Vascularity: It is subdivided into three different areas:

3a. It refers to the central demarcated area of the bleb as described in 1a

3b. It refers to the bleb area as described in 1b. When there is no peripheral part as in an encysted bleb, the margin between the central area and the non bleb conjunctiva should be described.

3c. It refers to the peripheral non bleb conjunctiva. If the bleb area is 100 % then it should be graded same as 3b.

Then each area is compared to a standard photograph and graded as follows:

1- Avascular
2- Normal vascularisation
3- Mild vascular inflammation
4- Moderate vascular inflammation
5- Severe vascular inflammation

Subconjunctival hemorrhage is noted as follows:

Yes- If subconjunctival blood is more than the scleral trap door.

No- If subconjunctival blood is less than the scleral trap door or absent.

**Wurzburg classification** (182-184) evaluates three parameters of bleb morphology which are avascualrity, corkscrew vessels and microcysts.

Avascularity and corkscrew vessels are scored from 0-3 as follows:

0- Entire bleb

1- 2/3 rd of bleb

2- 1/3 rd of bleb

3- None

Microcysts are classified from 0-3 as follows:

0- None

1- Over the sclera flap

2- Lateral and medial to the sclera flap

3- Entire bleb

**Indiana bleb appearance grading scale:** (185) This grading system is comparing four different parameters of bleb morphology with standard photographs. It includes-

1- Standards for bleb height

2- Standards for extent

3- Standards for vascularity

4- Standards for seidel's test

# MATERIALS AND METHODS

**Study design:**

Randomized, parallel group, active controlled trial

**Sample size calculation:**

The sample size was calculated based on a previous study by Rosentreter et al., (8) which compared MMC versus Ologen in trabeculectomy. The primary outcome of this study was reduction in IOP. From the previous study, we found that the mean reduction in IOP in the MMC group was 11.5mm Hg (SD= 4.1mmHg) and in the Ologen was 15.6 mm Hg (SD= 2.4mm Hg). To estimate a difference of 4 mmHg with a power of 80% and 5% level of significance, we calculated a total sample size of 60 (30 in each group). Considering lost to follow up rate of 5%, a sample size of 63 patients was obtained.

**Setting:**

This was a randomized controlled trial conducted from December 2011 to November 2012. The study was conducted in the Department of Ophthalmology, Christian Medical College, Vellore.

**Inclusion criteria:**

Patients attending the general outpatient department and the glaucoma clinic who required treatment with standard phacotrabeculectomy as decided on clinical evaluation by the glaucoma specialists were invited for the study. It included patients with:

- POAG
- PEX Glaucoma
- Pigmentary Glaucoma
- Steroid induced glaucoma
- Angle Closure Glaucoma
- NTG
- OHT

- Subject able and willing to cooperate with investigation plan.
- Subject able and willing to complete postoperative follow-up requirements.
- Subject willing to sign informed consent form.

**Exclusion criteria:**

- Ocular infection within 14 days prior to surgery.
- Glaucoma types which are more amenable to undergo primary valve repair will not be included. It includes:
  - NVG
  - Uveitic glaucoma
  - Pupillary block glaucoma secondary to subluxated lens

- Previous ocular surgery.

Patients fulfilling the above inclusion and exclusion criterion and willing to participate in the study by signing the consent (Appendix C, E- Consent in English and Tamil) were recruited into the study.

**Institutional Review Board approval**

The study protocol was approved by the Institutional Review Board which constituted members outside the institution as per the ICMR guidelines required for any study conducted in the institution. (Appendix A- IRB approval)

**Method of randomization:**

Block randomization technique with variable block sizes of 4, 6 and 8.

**Method of allocation concealment:**

Opaque sealed envelopes were used to conceal the sequence of random allocation. The envelopes were opened after recruitment of the participant into the study.

**Preoperative examination:**

After relevant history including the use of antiglaucoma medications, each patient underwent comprehensive eye examination by slit lamp biomicroscopy and indirect ophthalmoscopy which included:

- Best Corrected Visual Acuity using Snellen's visual acuity chart
- Anterior chamber depth by Von Herrings test
- Pupillary reaction to assess Relative Afferent Pupillary Defect

- Recording IOP by Goldmann applanation tonometer on atleast two different occasions
- Gonioscopy by Goldmann 2 mirror or Sussmann 4 mirror
- Fundus examination by 78 D lens and disc size assessment using a correction factor of 1.1
- Central corneal thickness(CCT) measurement using ultrasound pachymetry
- Standard automated perimetry (Humphrey Visual Field Analyser) using 24-2 or 30-2 SITA Standard protocol and 10-2 and macular program where indicated

**Target IOP:**

Prior to randomization of the patient, the target IOP was decided by the operating surgeon based on the extent of glaucomatous disc changes, severity of field defects, baseline IOP , age of the patient and the CCT.

**Definition of success:**

IOP within + 2mm Hg of target IOP

**Definition of failure:**

IOP more than +2 mmHg of target IOP and /or IOP ≤ 6 mm Hg (hypotony and hence defined as failure)

**Technique of surgery:**

All patients underwent two site combined trabeculectomy and phacoemulsification surgery with implantation of foldable intraocular lens under peribulbar anesthesia. The surgery was performed by one of four glaucoma specialists according to the standard surgical technique as described below. MMC or Ologen was used as per the randomization. MMC was used in a concentration of 0.4 mg/ml and Ologen implant model 83601 was used.

Steps of surgery are described as shown below:

- Dressing and draping was done to ensure sterility of the operating field and superior rectus bridle suture applied.
- Superior fornix based conjunctival peritomy was done using blunt tipped Westcott scissors.
- Cauterization was done meticulously by monopolar cautery.
- In the MMC group, after peritomy 3 sponges soaked in 0.4mg/ml of MMC was placed under the conjunctiva for duration of 90 seconds. It was then thoroughly irrigated with balanced salt solution.
- A rectangular partial thickness sclera flap ($2/3^{rd}$ depth of scleral thickness) was made.
- Using a clear corneal incision at a separate site, cataract extraction was done by routine phacoemulsification with foldable Intraocular lens implantation.
- Pupil was constricted with intracameral pilocarpine if required.
- Under the scleral flap, the trabecular block excision was done using superblade and angled Vann's scissors or a Kelly Descemet's punch.

- Peripheral iridectomy was done by grasping the iris tissue through the trabecular block and excising it with Vanna's scissors keeping it parallel to the limbus.
- 1 releaseable suture and one fixed sclera flap suture were placed at the upper corners of the rectangular scleral flap.
- In patients randomized to Ologen, the Ologen implant was placed such that the anterior end of the implant rested at the posterior border of the rectangular scleral flap.
- The conjunctiva was closed with wing sutures and one mattress suture.

**Follow up:**

All patients were followed up as per schedule shown below:

- Day 1
- Week 1 ± 3 days
- 6 Week ± 5days
- 3 Month ± 1 week

Most patients were discharged from the hospital on the fifth post-operative day. The examination during each follow up included:

- Best Corrected Visual Acuity by Snellens chart
- Bleb morphology assessment and grading by Moorfields grading system as described in Review of literature.

- Seidel's test
- Anterior chamber depth assessment by Von Herrick's test
- IOP by Goldmann applanation tonometer
- Fundus examination with 78 D/20D indirect ophthlamoscopy
- Postoperative antiglaucoma medications if needed
- Postoperative wound modification required was noted: 5FU injections, laser suturolysis, bleb massage, releaseable release, needling. Injection 5-FU in a dose of 5mg in 0.1 ml was given subconjunctivally above the site of bleb to patients if the bleb was found to be vascular. Bleb massage was given as and when needed to keep the bleb formed. External bleb needling was done if the bleb was encysted / flat due to fibrosis.

**Statistical analysis:**

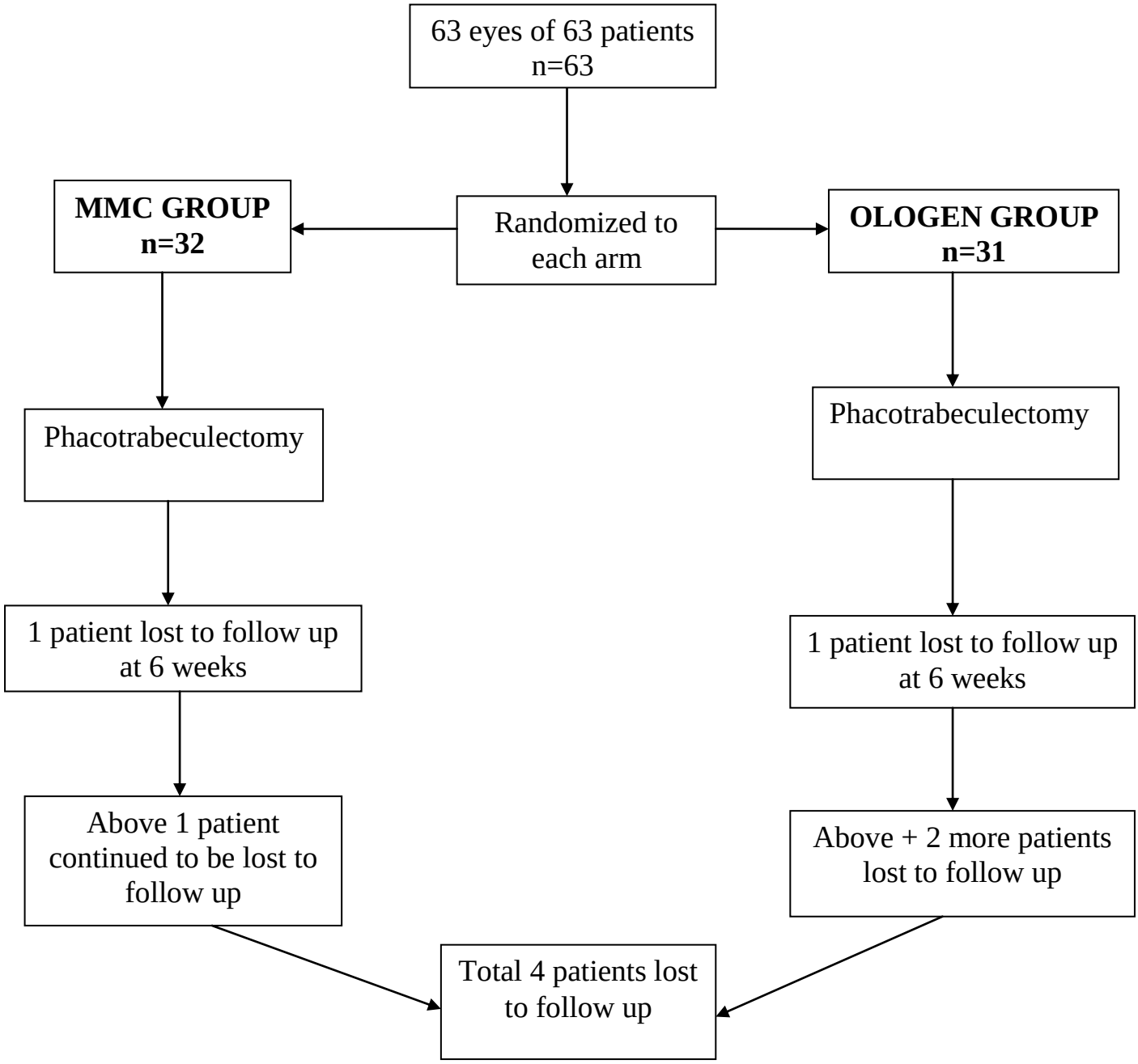
The collected data was compiled on Microsoft Excel Spreadsheet and was analyzed with the aid of SPSS data analysis software version 17.0.

Analysis of the baseline characteristics of each group was done using cross tab tables and the significance was determined using Chi square test.

Success and failure in each group was also compared using Chi square test. All the evaluations were done at 6 weeks and 3 months follow up period. The rate of complications, additional interventions, bleb morphology characteristics and number of injections of 5-FU were also evaluated using Chi square test. The comparison in between the two groups was done by Mann Whitney test.

## RESULTS

Patients were recruited and followed up as per the flow chart shown below:



A total number of 63 patients (table 10) were included in the study. They were randomized to phacotrabeculectomy with either MMC or Ologen implant.

**Table 10: Number of patients in the two groups**

| **MMC** | **Ologen** |
|---|---|
| 32 | 31 |

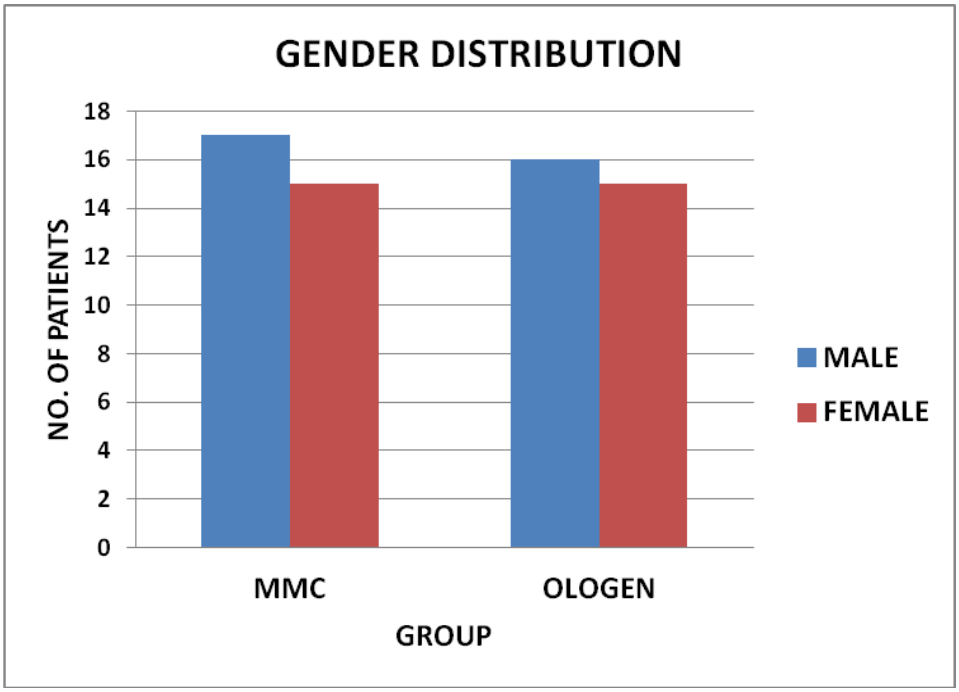
The baseline characteristics of the two groups of patients are described under the following headings. There was no statistically significant difference in the baseline demographics of the patients.

1. **Gender distribution:** Gender distribution in the two groups is shown in table 11 and figure 1.

**Table 11: Gender distribution in the two groups**

| | **Male (%)** | **Female (%)** | **Total (%)** |
|---|---|---|---|
| **MMC** | 17(53.13) | 15(46.88) | 32(100.00) |
| **Ologen** | 16(51.61) | 15(48.39) | 31(100.00) |
| **Total** | 33(52.38) | 30(47.62) | 63(100.00) |

**Figure 1: Graph showing the gender distribution in the two groups**

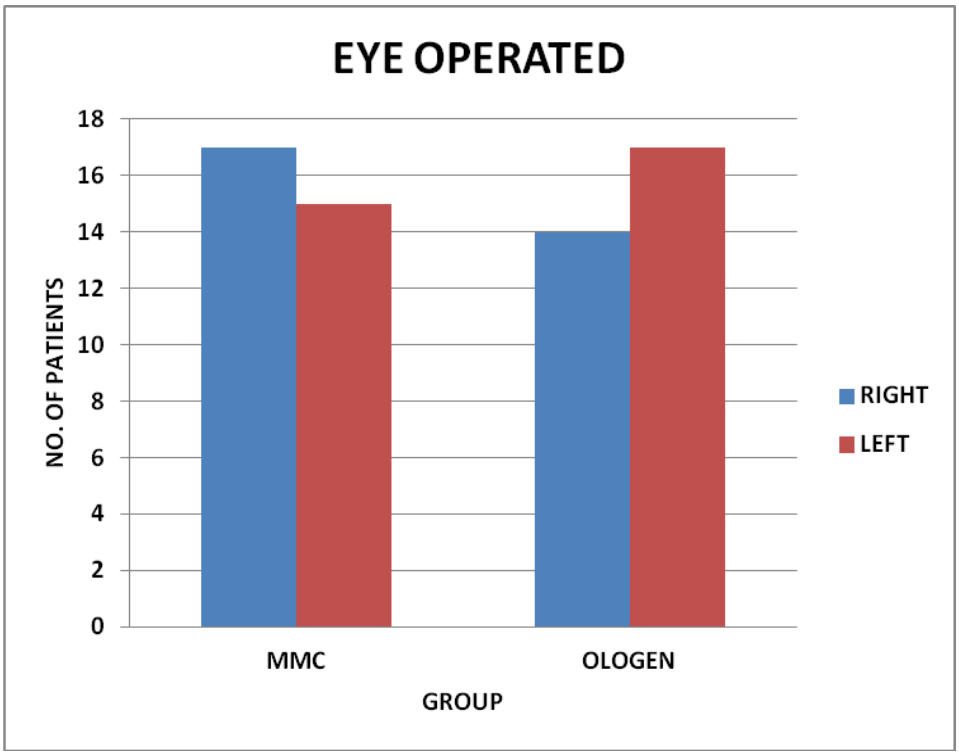


2. **Eye operated:** The frequency of the eye operated in the two groups are shown in table 12 and figure 2.

**Table 12: Frequency of the eye (right/left) operated in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **Right** | 17(54.84) | 14(45.16) | 31(100.00) |
| **Left** | 15(46.88) | 17(53.13) | 32(100.00) |
| **Total** | 32(50.79) | 31(49.21) | 63(100.00) |

**Figure 2: Graph showing the distribution of the eye (right/left) operated in the two groups**



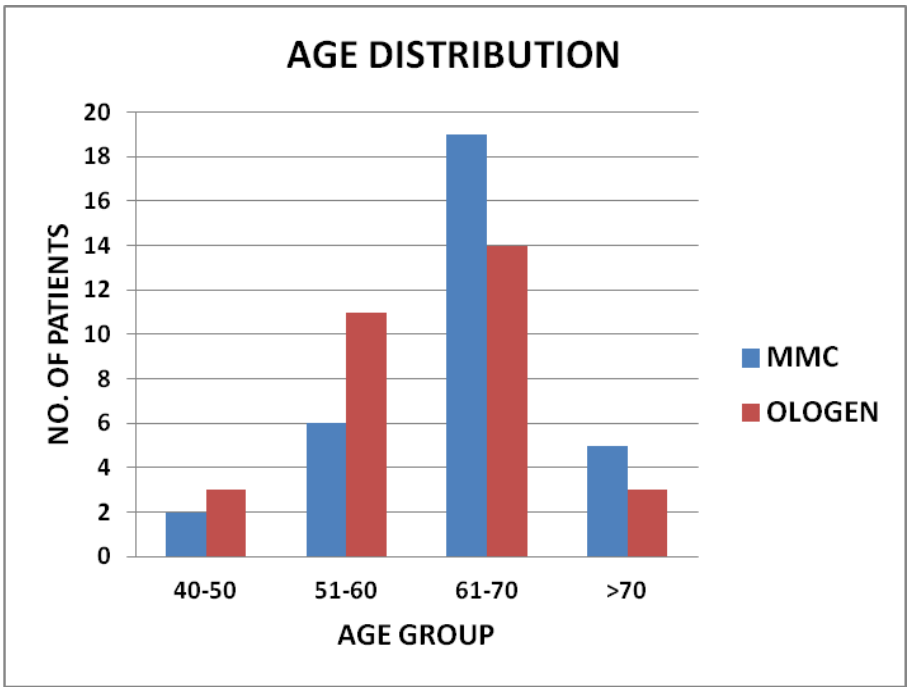
### 3. Age distribution

Table 13 and figure 3 show the decade wise age distribution in the two groups. More than 50% of patients were in the age group 61-70 years. The second most common age group was 51-60 years.

**Table 13: Distribution of patient across different age groups in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **40-50** | 2 (6.45) | 3(9.37) | 5(7.94) |
| **51-60** | 6 (19.35) | 11(34.37) | 17(26.98) |
| **61-70** | 19 (61.29) | 14(43.75) | 33(52.38) |
| **>70** | 5 (16.13) | 3(9.37) | 8(12.70) |
| **Total** | 31 | 32 | 63 |

**Figure 3: Graph showing the age distribution of patients in the two groups.**



## 4. Diagnosis

POAG was the most common diagnosis. The next most common diagnosis was NTG. There was no statistically significant difference in between the two groups in the distribution of different diagnoses although more patients with NTG were in the MMC group. Table 14 and Figures 4, 5, 6 show the distribution of the types of glaucoma diagnosed in the two study groups.

**Table 14: Distribution of the various diagnoses in the two groups**

| | POAG(%) | NTG(%) | PACG(%) | PEX glaucoma(%) | OHT(%) | Total(%) |
|---|---|---|---|---|---|---|
| **MMC** | 11(34.38) | 14(43.75) | 3(9.38) | 3(9.38) | 1(3.13) | 32(100.00) |
| **Ologen** | 16(51.61) | 7(22.58) | 3(9.68) | 3(9.68) | 2(6.45) | 31(100.00) |
| **Total** | 27(42.86) | 21(33.33) | 6(9.52) | 6(9.52) | 3(4.76) | 63(100.00) |

**Figure 4: Pie diagram showing the distribution of the various types of glaucoma among the subjects in the MMC group**

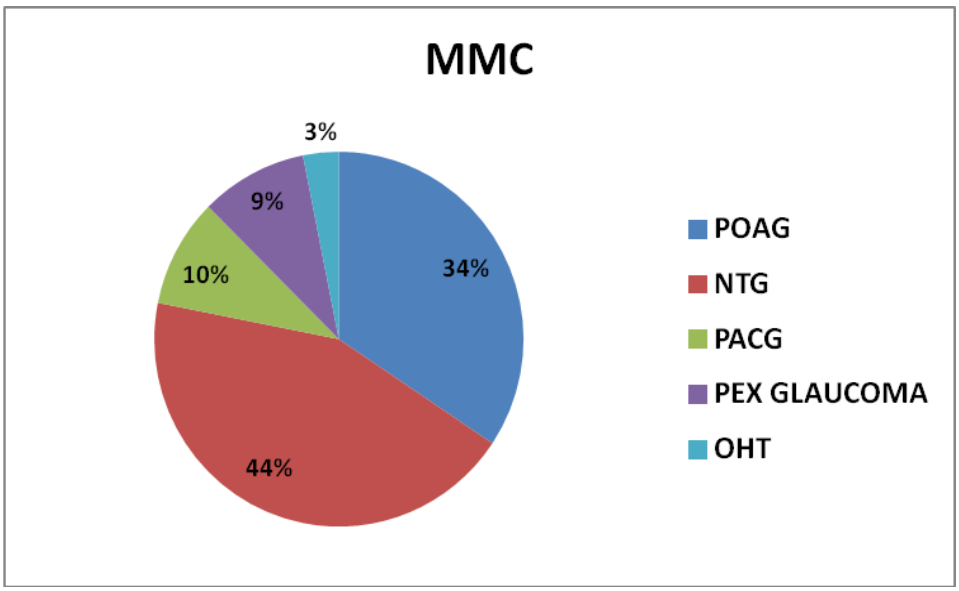


**Figure 5: Pie diagram showing the distribution of the various types of glaucoma among the subjects in the Ologen group**

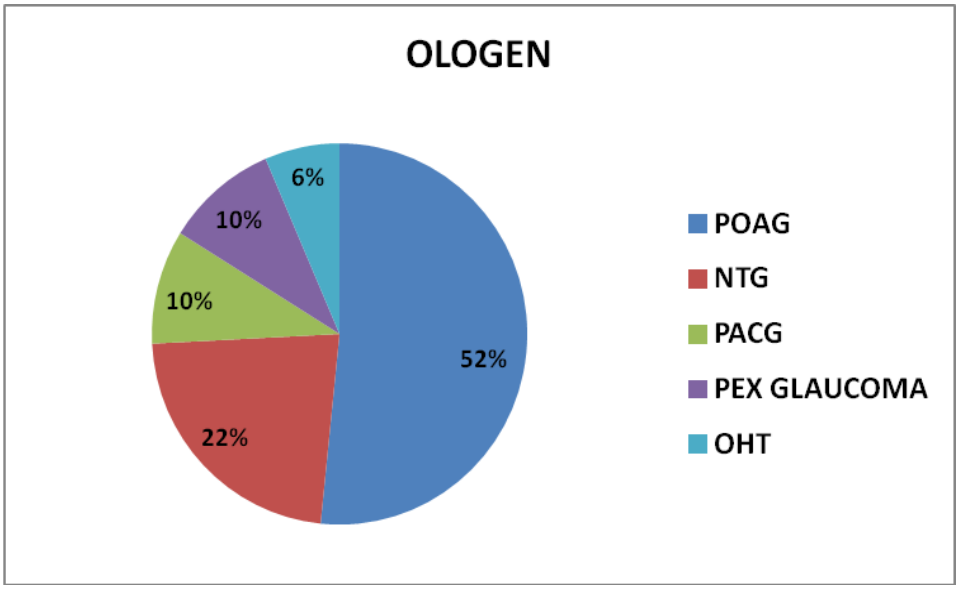
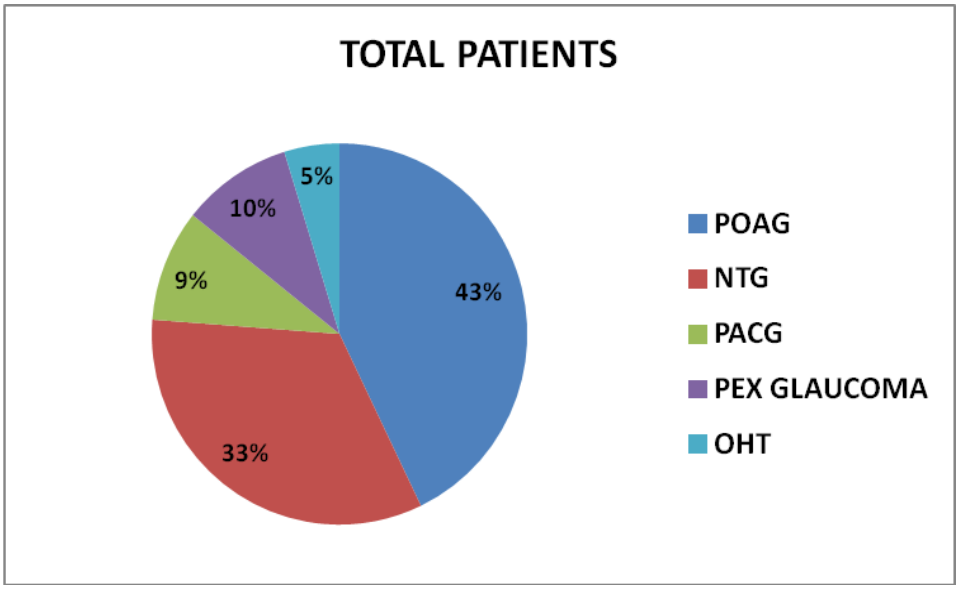



**Figure 6: Pie diagram showing the distribution of the various types of glaucoma in the entire study group (MMC and Ologen) group**



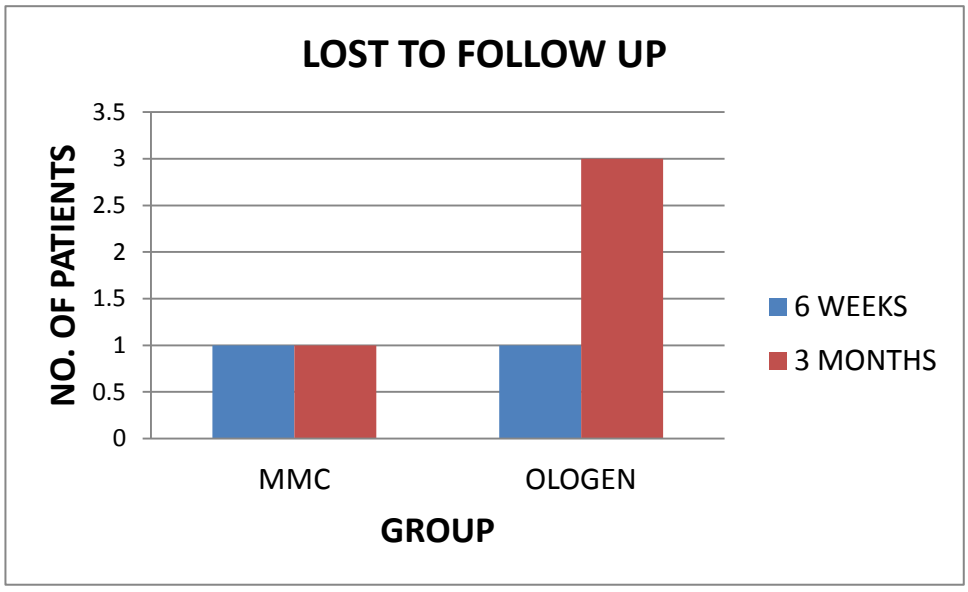
## 5. Lost to follow up

At the end of 6 weeks 1 patient was lost to follow up in each group.4 patients were lost to follow up at 3 months. Details of the lost to follow up patients are given in table 15 and figure 7.

**Table 15: Details of patients lost to follow up at 6 weeks and at 3 months in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **6 weeks** | 1(3.23) | 1(3.12) | 2(3.17) |
| **3 months** | 1(3.23) | 3(9.37) | 4(6.35) |

**Figure 7: Graph showing patients lost to follow up in each group**



## 6. Preoperative IOP

There was no statistically significant difference between the preoperative IOP in between the two groups (p value=0.06). It is shown in table 16 below. As we saw above NTG comprised about 44% patients in MMC group while POAG comprised 52% patients in Ologen group. Therefore mean IOP was higher in the Ologen group but it did not affect the results as success was defined for each case individually based on target IOP as detailed under the section of 'materials and methods'.

**Table 16: Mean preoperative IOP in the two groups**

| **MMC (mm Hg)/ Mean±SD** | **Ologen (mm Hg)/ Mean±SD** |
|---|---|
| 20.55 ± 6.42 | 23.97 ± 10.42 |

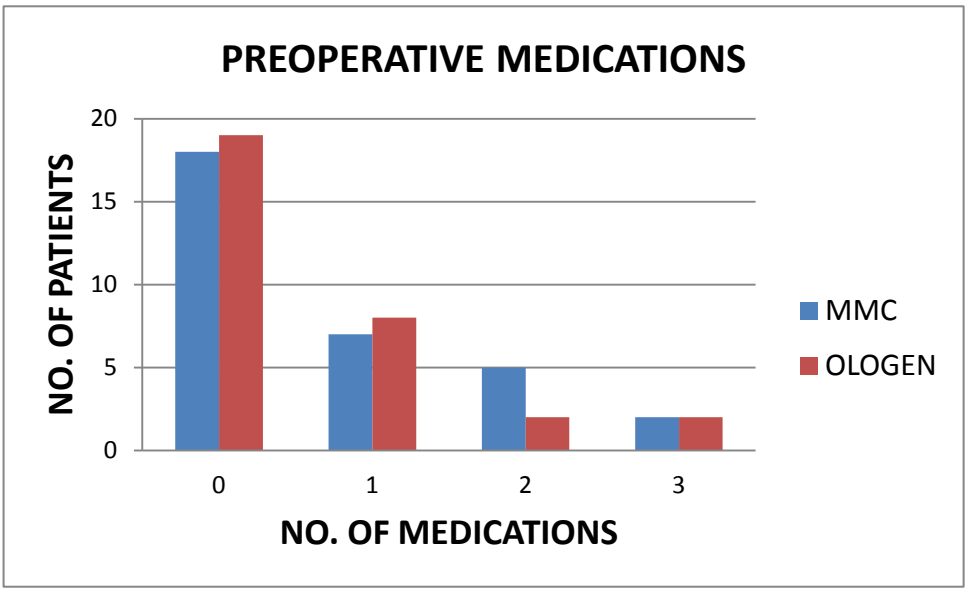
### 7. Number of preoperative medications

As shown below 58.73% were not on any preoperative medication while 6.35% patients were on 3 different subgroups of antiglaucoma medications. The details about the number of medications are shown in table 17 and figure 8. There was no statistically significant difference between the two groups (p= 0.714).

**Table 17: Distribution of patients 'on' or 'not on' antiglaucoma medications pre-operatively in the two groups**

| | Patients on no medication (%) | Patients on single medication (%) | Patients on two medications (%) | Patients on three medications (%) | Total |
|---|---|---|---|---|---|
| **MMC** | 18(56.25) | 7(21.88) | 5(15.63) | 2(6.25) | 32(100.00) |
| **Ologen** | 19(61.29) | 8(25.81) | 2(6.45) | 2(6.45) | 31(100.00) |
| **Total** | 37(58.73) | 15(23.81) | 7(11.11) | 4(6.35) | 63(100.00) |

**Figure 8: Graph showing preoperative medications in the two groups**



## 8. Outcome at 6 weeks

80% of the patients in the MMC group achieved target IOP at 6 weeks as compared to 70% in the Ologen group (0.334). However this difference was not statistically significant. The details of the IOP are shown in table 18, 19 and figure 9.

**Table 18: Success and failures in the two groups at 6 weeks**

| | **Success (%)** | **Failure (%)** | **Total (%)** |
|---|---|---|---|
| **MMC** | 25(80.65) | 6(19.35) | 31(100.00) |
| **Ologen** | 21(70.00) | 9(30.00) | 30(100.00) |
| **Total** | 46(75.41) | 15(24.59) | 61(100.00) |

**Figure 9: Graph showing the distribution of success and failure in the two groups at 6 weeks**

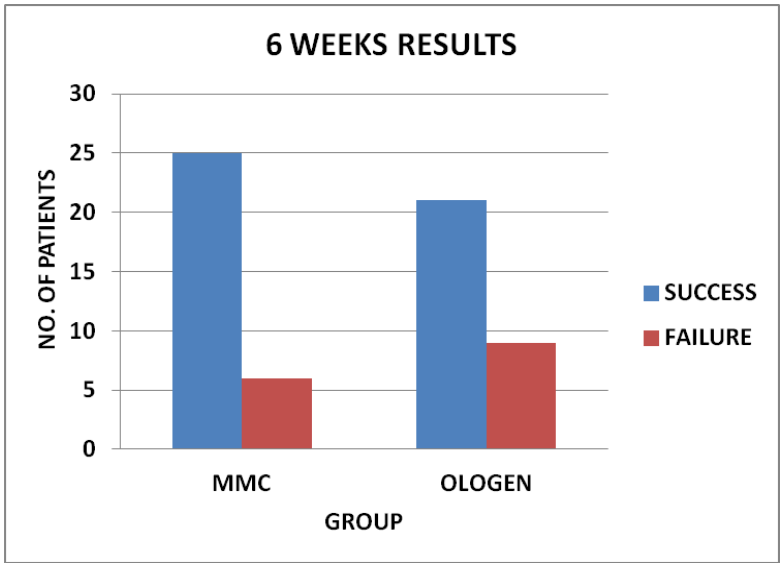


**Table 19: Mean IOP in the study groups at baseline and at 6 weeks**

| | MMC (mm Hg) | Ologen (mm Hg) |
|---|---|---|
| **Baseline IOP** | 20.55 ± 6.42 | 23.97 ± 10.42 |
| **6 weeks IOP** | 11.93 ± 5.20 | 13.52 ± 4.64 |

The mean reduction in IOP in MMC group and Ologen group was 8.47 ± 6.77 mm Hg and 10.33 ±10.86 mm Hg respectively. Both were statistically significant drop from the baseline ($p<0.001$). The reduction in IOP in between the two groups was not statistically significant ($p = 0.268$).

**9. Outcome at 3 months**

By the end of 3 months.87.1% of the patients in the MMC group achieved target IOP as compared to 88.14% in the Ologen group (p=0.795). The details of the IOP are shown in table 20, 21and figure 10.

**Table 20: Success and failures in the two groups at 3 months**

| | Success (%) | Failure (%) | Total (%) |
|---|---|---|---|
| **MMC** | 27(87.10) | 4(12.90) | 31(100.00) |
| **Ologen** | 25(89.29) | 3(10.71) | 28(100.00) |
| **Total** | 52(88.14) | 7(11.86) | 59(100.00) |

**Figure 10: Graph showing the distribution of success and failure in the two groups at 3 months**

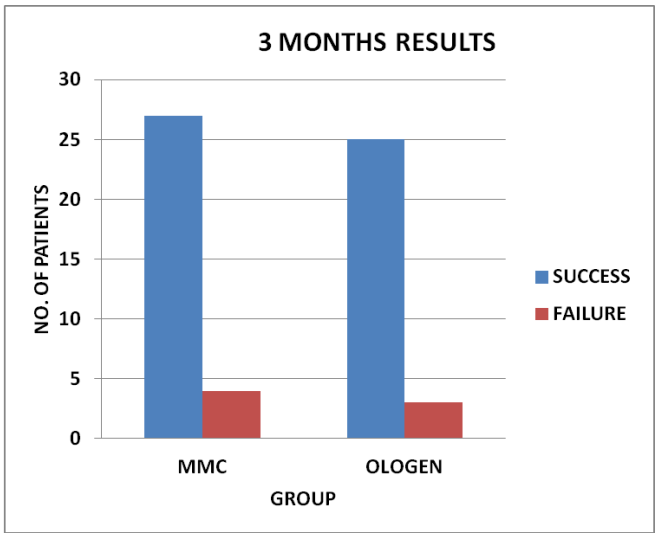



**Table 21: Mean IOP in the study groups at baseline and at 3 months**

| | MMC(mm Hg)/ Mean ± SD | Ologen(mm Hg)/ Mean ± SD |
|---|---|---|
| **Baseline** | 20.55 ± 6.42 | 23.97 ± 10.42 |
| **3 months** | 12.39 ± 3.3 | 13.18 ± 4.3 |

There was no statistically significant difference in the mean postoperative IOP (p value = 0.47). The mean reduction of IOP from baseline to 3 months was 8 ± 6.5 mm Hg in MMC group and 10.8 ± 9.8 mm Hg in the Ologen group. The reduction in IOP from baseline was significant in each group ($p<0.001$). The reduction in IOP from baseline in between the two groups was not statistically significant (p value=0.20).

**10. Number of postoperative medications:**

4 patients in MMC group and 3 patients in the Ologen group did not achieve success as defined in the study. However only 1 patient had to be started on timolol drops in the MMC group as the IOP was not controlled. It was not statistically significant (p = 0.338). In the rest of them, though target IOP was not achieved, there was reduction in the IOP following surgery. After reassessing the morphology of the optic nerve head it was decided to defer treatment till further follow up. These patients were planned for further follow up with IOP and fields after 3 months and decision of need for medications based on IOP and progression if any. The details of postoperative medications is shown in table 22.

**Table 22: Details of post operative anti-glaucoma medications at 3 months**

| | **Patients on no medication (%)** | **Patients on single medication (%)** | **Total** (%) |
|---|---|---|---|
| **MMC** | 30(96.77) | 1(3.23) | 31(100.00) |
| **Ologen** | 28(100.00) | 0(0.00) | 28(100.00) |
| **Total** | 58(98.31) | 1(1.69) | 59(100.00) |

**11. Complications:**

No complications were seen in 86.44% cases. There was no statistically significant difference in the rate of complications in between the two groups. The details are described in table 23 and figure 11.

**Table 23: Distribution of various complications in the two groups**

| | **MMC (%)** | **Ologen (%)** | **P value** |
|---|---|---|---|
| **Hypotony** | 4 (12.90) | 1 (3.57) | 0.199 |
| **Hypotonic maculopathy** | 1(3.23) | 1(3.57) | 0.942 |
| **Choroidal detachment** | 3(9.68) | 0(0.00) | 0.091 |
| **Leak** | 2 (6.45) | 1 (3.57) | 0.615 |

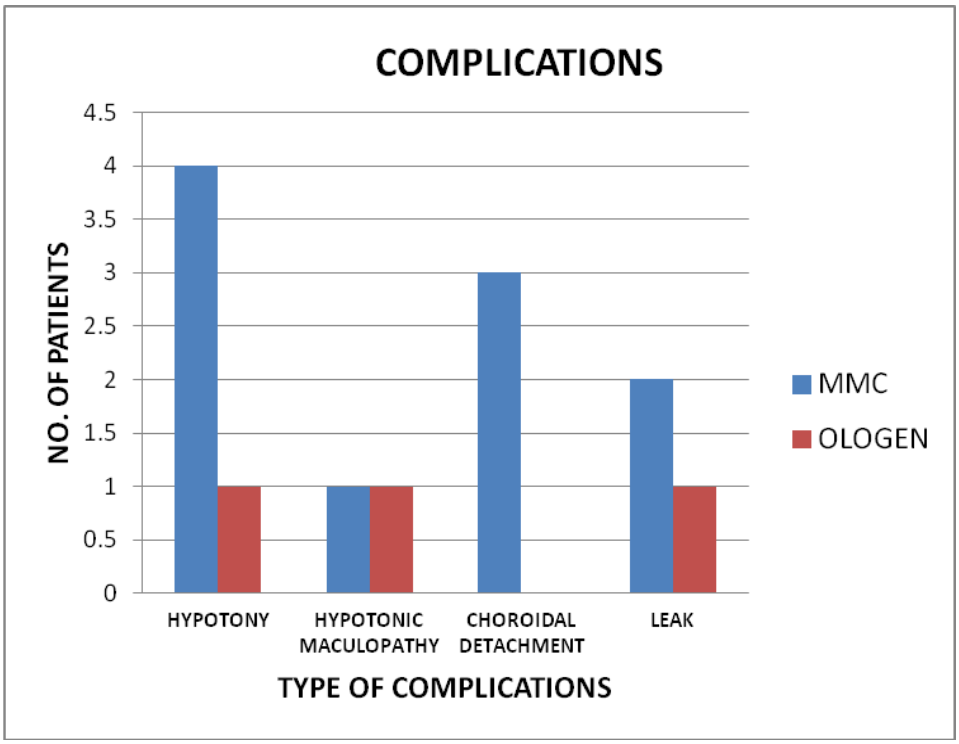
- **Hypotony:** 4 patients had hypotony in the MMC group as compared to only 1 patient in the Ologen group.Of the four patients who had hypotony in the MMC group, only one patient had persistent hypotony at 3 months. In the Ologen group, the one patient with hypotony did not recover at 3 months follow up. However, both the patients did not have associated hypotonic maculopathy.

- **Leak:** The 2 patients in MMC group had associated transient choroidal detachment which resolved spontaneously. 1 of these patients required conjunctival resuturing. 1 patient in the Ologen group had associated transient hypotonic maculopathy.

- **Hypotonic maculopathy:** In 2 patients hypotonic maculopathy was only transient which resolved spontaneously.

- **Choroidal detachment**: In 2 patients it was associated with wound leak, 1 patient required conjunctival resuturing. In 2 patients it was associated with transient hypotony which resolved spontaneously without any intervention.

**Figure 11: Graph showing distribution of complications in the two groups**



**12. Additional interventions - Needling**

Needling with injection 5-FU was done in 3 patients in MMC group and 1 patient in Ologen group. Needling resulted in achieving the desired IOP in all patients in the MMC group. One of these patients developed dense exudative reaction and shallow anterior chamber after needling due to seepage of 5-FU into anterior chamber. He underwent anterior chamber reformation. In the Ologen group only one patient needed to undergo needling at 3 month follow up and the needling achieved success on subsequent follow up visit.

13. **Additional intervention - Resuturing:**

One patient in the MMC group required conjunctival resuturing as it was associated with bleb leak.

**14. Additional intervention – Injection 5 -FU**

During the study period, 53 patients received 5FU in the MMC and 46 patients in the ologen group. There was no statistically significant difference in between the MMC and Ologen group (p value= 0.53) and also those who achieved success and who failed (p value=0.47). This was calculated using the Chi Square test. It is described in detail in table 24.

**Table 24: Requirement of 5-FU in the MMC and Ologen groups**

| | **MMC success (%)** | **MMC failure (%)** | **Ologen success (%)** | **Ologen failure (%)** |
|---|---|---|---|---|
| **No. of patients requring 5-FU** | 20 | 4 | 19 | 2 |
| **No. of patients not requring 5-FU** | 7 | 0 | 6 | 1 |
| **Total no. of 5-FU** | 44 | 9 | 41 | 5 |
| **Total no. of 5-FU** | 53 in MMC | | 46 in Ologen | |
| **No. of 5-FU per patient** | 1.71 | | 1.64 | |

## 15. Assessment of bleb morphology

Analysis of bleb morphology was done at 3 months between the two groups - MMC and Ologen. Bleb morphology included bleb area score, bleb height and vascularity score as explained in the review of literature section. The photographs are shown in the Appendix H. No. of patients in each scoring level was calculated in both the Ologen and MMC group. No statistically significant difference was found between any of the categories. It was calculated usimg Chi square test and Mann Whitney test. Comparison of the bleb morphology between the two groups is shown in table 25-30 and figure 12-17.

**Table 25: Bleb morphology – Scoring of the "central demarcated area-1a" in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **1** | 1 (3.23) | 0 (0.00) | 1 (1.69) |
| **2** | 12 (38.71) | 12 (42.86) | 24 (40.68) |
| **3** | 16 (51.61) | 16 (57.14) | 32 (54.24) |
| **4** | 2 (6.45) | 0 (0.00) | 2 (3.39) |
| **5** | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| **Total** | 31 (100.00) | 28 (100.00) | 59 (100.00) |

**Figure 12: Graph showing scoring of the "central demarcated area-1a" in the two groups**

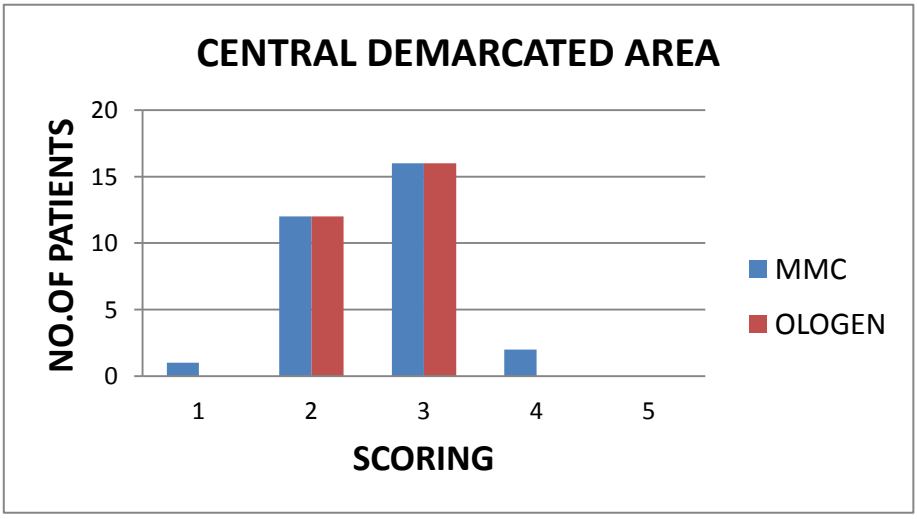


**Table 26: Bleb morphology– Scoring of the "maximal area-2a" in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **1** | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| **2** | 11 (35.48) | 6 (21.43) | 17 (28.81) |
| **3** | 17 (54.84) | 22 (78.57) | 39 (66.10) |
| **4** | 3 ( 9.68) | 0 (0.00) | 3 (5.08) |
| **5** | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| **Total** | 31 (100.00) | 28 (100.00) | 59 (100.00) |

**Figure 13: Graph showing scoring of the "maximal area-2a" in the two groups**

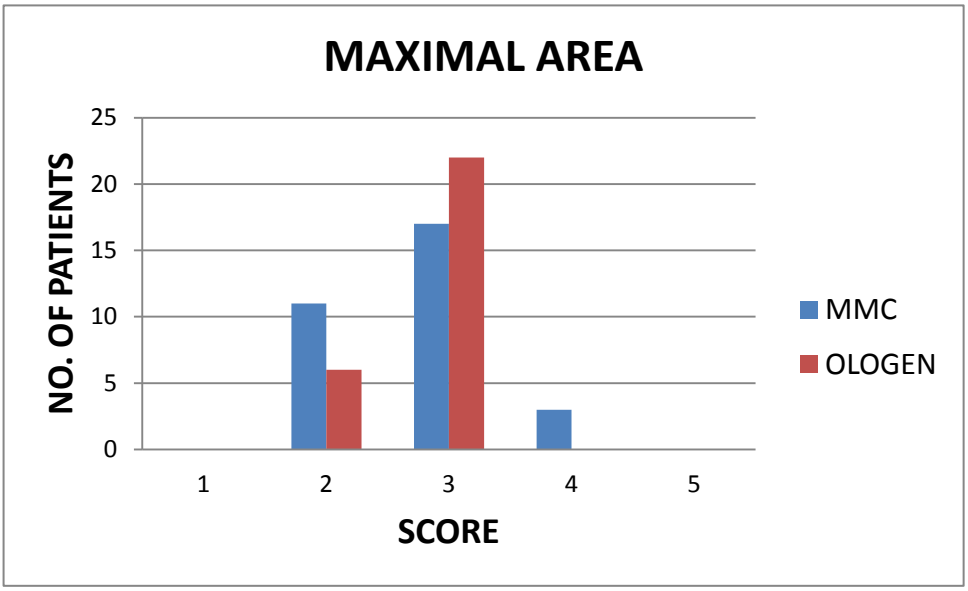


**Table 27: Bleb morphology – Scoring of the "bleb height" in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **1** | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| **2** | 18 (58.06) | 10 (35.71) | 28 (47.46) |
| **3** | 13 (41.94) | 18 (64.29) | 31 (52.54) |
| **4** | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| **Total** | 31 (100.00) | 28 (100.00) | 59 (100.00) |

**Figure 14: Graph showing scoring of the "bleb height" in the two groups**

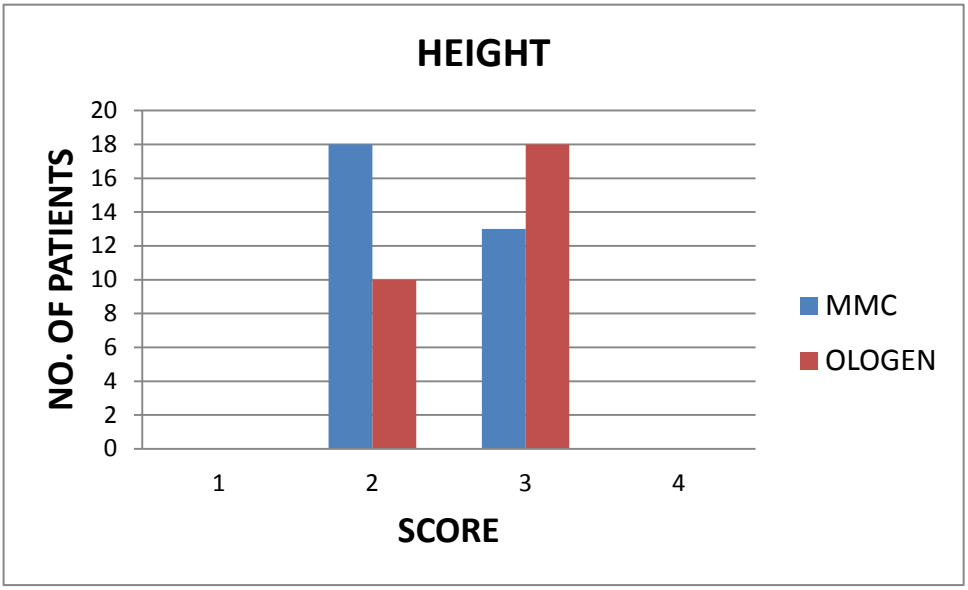


**Table 28: Bleb morphology – Scoring of the "vascularity central demarcated area-3a" in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **1** | 3 (9.68) | 1 (3.57) | 4 (6.78) |
| **2** | 11 (35.48) | 13 (46.43) | 24 (40.68) |
| **3** | 14 (45.16) | 7 (25.00) | 21 (35.59) |
| **4** | 3 (9.68) | 7 (25.00) | 10 (16.95) |
| **5** | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| **Total** | 31 (100.00) | 28 (100.00) | 59 (100.00) |

**Figure 15: Graph showing scoring of the "vascularity central demarcated area-3a" in the two groups**

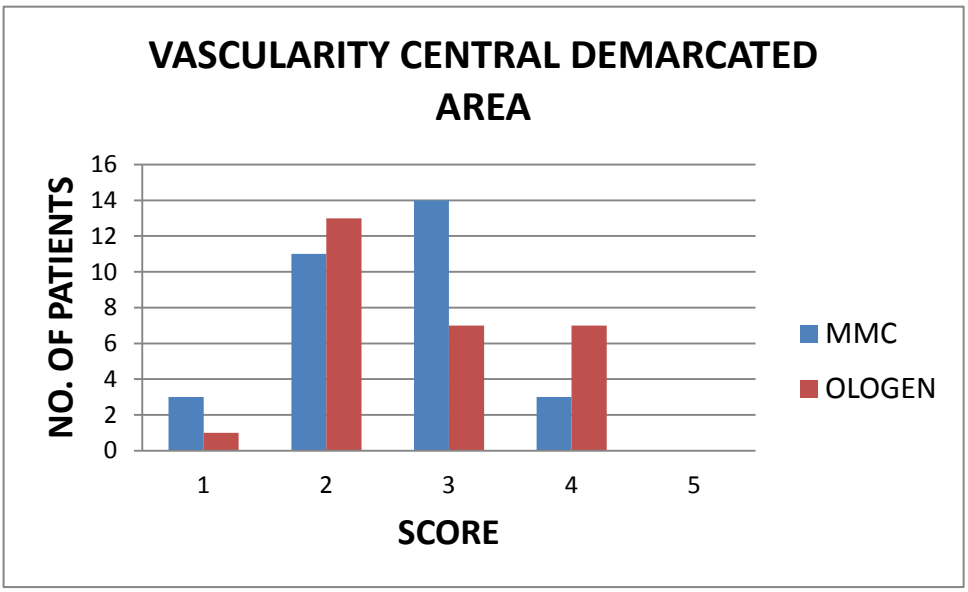


**Table 29: Bleb Morphology – Scoring of the "vascularity maximal area-3b" in the two groups**

| | MMC (%) | Ologen (%) | Total (%) |
|---|---|---|---|
| **1** | 1 (3.23) | 0 (0.00) | 1(1.69) |
| **2** | 14(45.16) | 14(50.00) | 28(47.46) |
| **3** | 13(41.94) | 8(28.57) | 21(35.59) |
| **4** | 3(9.68) | 5(17.86) | 8(13.56) |
| **5** | 0 (0.00) | 1(3.57) | 1(1.69) |
| **Total** | 31 (100.00) | 28 (100.00) | 59 (100.00) |

**Figure 16: Graph showing scoring of the "vascularity maximal area-3b" in the two groups**

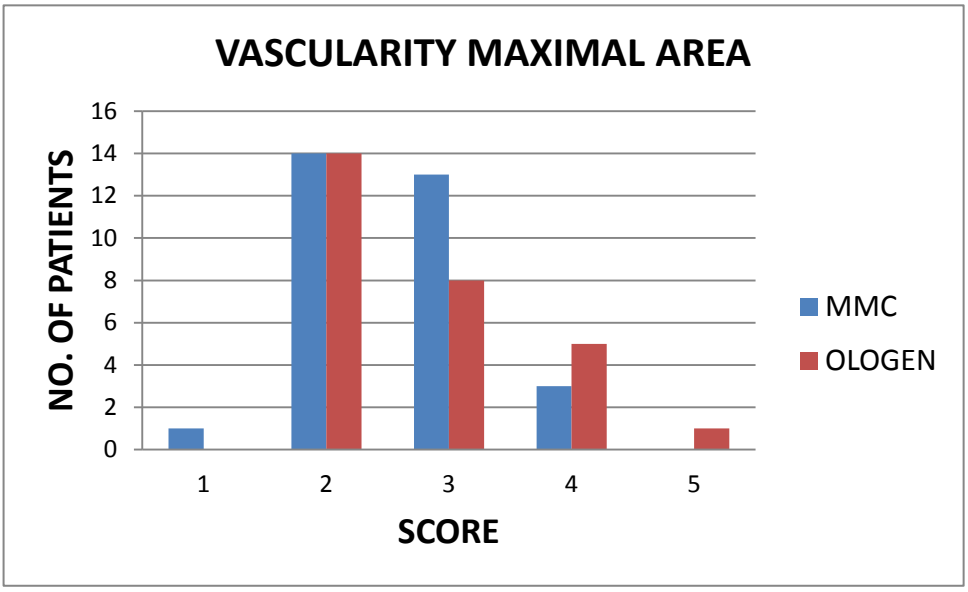
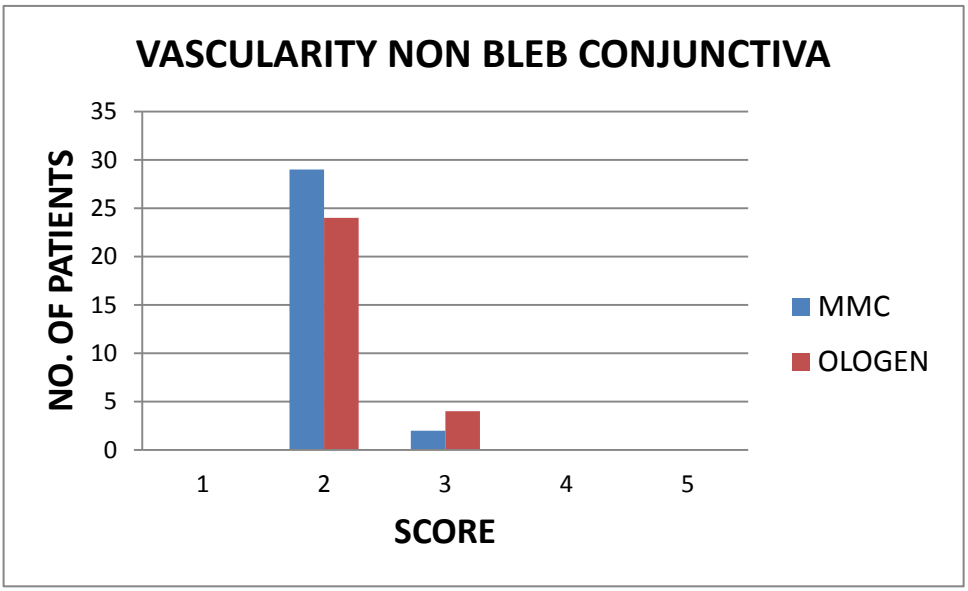


**Table 30: Bleb morphology – Scoring of the "vascularity non bleb conjunctiva-3c" in the two groups**

| | MMC (%) | OLOGEN (%) | TOTAL (%) |
|---|---|---|---|
| 1 | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| 2 | 29 (93.55) | 24 (85.71) | 53 (89.83) |
| 3 | 2 (6.45) | 4 (14.29) | 6 (10.17) |
| 4 | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| 5 | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| TOTAL | 31 (100.00) | 28 (100.00) | 59 (100.00) |

**Figure 17: Graph showing scoring of the "vascularity non bleb conjunctiva -3c" in the two groups**




**Subconjunctival Blood:** At 3 months follow up none of the patients had subconjunctival hemorrhage.

## DISCUSSION

The primary aim of this study was to compare the safety and efficacy of MMC versus Ologen implant in phacotrabeculectomy surgery. 63 patients were randomized by block randomization, to phacotrabeculectomy with either MMC (32 patients) or Ologen implant (31 patients). We included patients with POAG, NTG, PACG, PEX Glaucoma and OHT. Other similar studies (6-9) have not included NTG and OHT.

Different studies (6-9) have used different concentrations of MMC (0.2- 0.4 mg/ml) and different durations of application (2-3 min) . We used 0.4mg/ml MMC for 90 seconds. This is the concentration and duration that is routinely used in our institution with adequate success and less complications in our population.

Ologen implant (model number-830601) with dimensions of 6mm x 2mm was used in our study. Marey et al., (6) and Cillino et al., (7) used the same model of Ologen implant as our study. Boey et al., (9) used model number – 83068 with dimensions of 7mmx4mm. Rosentreter et al., (8) used implant of dimensions 7mmx4mm (model number has not been specified) which is version 1 subtype of ologen implant. We used this model as it made up of atelocolagen, which is supposed to have lower immunigenecity and additional anti-inflammatory action (173).

Surgical procedure was similar in both the groups. Standard two site phacotrabeculectomy was performed. All patients had one releaseable and one fixed scleral flap suture and a conjunctival mattress suture which is the routine surgical procedure performed in our institution. Unlike in some other studies, the scleral flap suture in the Ologen group was not

made loose (6-9).The use of a releasable suture ensured post-operative manipulation in the Ologen group where laser suturolysis is difficult to perform.

Use of 5-FU in phacotrabeculectomy with Ologen in RCTs (6-8) has not been described. In our study 5 FU was given to patients with increased vascularity of the belb as assessed by a glaucoma specialist irrespective of whether the patient belonged to MMC or Ologen group. We also looked at the difference in the requirement of post operative antifibrotics between the two groups. We studied bleb morphology using Moorfields bleb grading system. Marey et al., (6), Boey et al., (9) andCillino et al., (7) also studied bleb morphology using Moorfields bleb grading system. Rosentreter et al., (8) used Wurzberg bleb classification system.

We defined success based on target IOP as determined for each patient individually. Success was defined as IOP within + 2 mm Hg of target IOP and ≥6 mm Hg. IOP less than 6 mm Hg was considered to be hypotony. Different studies have defined absolute values (6-8) and reduction of IOPs (8-9) from baseline as success. We chose target IOP because we included patient with NTG in our study.

We initially calculated sample size considering 5% of patients being lost to follow up as 63. During the course of the study, we found an increase in the dropout rate (6.35%). The recalculated sample size for 10% drop out was 66. However these three patients have not completed 3 month follow up and hence not included in the analysis.

Both MMC and Ologen implant were equally effective in lowering IOP in phacotrabeculectomy surgery. There was no significant difference in the success rate between the two groups. In a similar study, Boey et al., (9) have found that MMC is more effective in

lowering IOP than Ologen implant after phacotrabeculectomy. However the duration of application of MMC in this study was longer (2 min) and a different model (83068) of Ologen implant was used. Rosentreter et al., (8) have also found MMC to be superior to Ologen in trabeculectomy. Here again the duration of MMC was 3 minutes and the size of the ologen implant used was larger. Studies by Cillino et al., (7)and Marey et al., (6)which used the same model of Ologen implant as ours (830601) have shown no difference between the two groups.

There was no significant difference in the additional interventions including the requirement of post operative 5 FU between the two groups. Other RCTs (6-8) comparing Ologen and MMC have not used 5FU.

The bleb morphology was similar in both groups in terms of bleb area, bleb height and bleb vascularity at 3 months. Marey et al., (6)and Rosentreter et al., (8) found more avascular blebs in the MMC group as compared to the ologen group at the end 1 year. However Cillino et al., (7) found no significant difference between the two groups at the end of 2 years in all the scores. Boey et al., (9) found more vascular blebs and bleb height being lower in the Ologen group at 2 month follow up.

Our study did not show any significant difference in the rate of complications between the two groups (Table 23). There were no serious complications in either group. Marey et al., (8), Rosentreter et al., (8) and Cillino et al., (7) similarly found no significant difference in the complication rates between the two groups.

MMC is associated with thin avascular blebs and late bleb leaks which can lead to blebitis and eventually sight threatening endophthalmitis (3-5). The use of Ologen may overcome this problem. However this would require long term follow up of Ologen patients with respect to success and bleb morphology. The main limitation of our study is the short term follow up. Longer follow up will help us to compare the long term success as well as complications of the 2 groups.

In view of the high costs of Ologen, its routine use would be justified only if we are able to establish, success rates similar to MMC with lesser incidence of thin walled and late leaking blebs on longer follow up. The longest follow up (2 years) study by Cillino et al., (7) showed similar bleb morphology and success rates in both groups. There was no increased incidence of thin walled blebs in the MMC group (0.2 mg for 2 minutes).

In conclusion, our study showed no significant difference between the two groups in terms of success, bleb morphology, additional interventions needed and complications. Ologen implant is as effective and safe as MMC in phacotrabeculectomy.

## CONCLUSIONS

- Both MMC and Ologen implant are equally efficacious in lowering IOP in phacotrabeculectomy surgery. There was no statistically significant difference between the success rates between the two groups at 6 weeks and 3 months follow up.
- There was no statistically significant difference in the bleb morphology between the two groups.
- The postoperative complications, need for additional interventions and antiglaucoma medications was similar in both the groups.

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# APPENDIX A - IRB APPROVAL LETTER


**INSTITUTIONAL REVIEW BOARD (IRB)**
**CHRISTIAN MEDICAL COLLEGE**
VELLORE 632 002, INDIA

**Dr. George Thomas, D Orth**
Editor, Indian Journal of Medical Ethics
Chairperson, Ethics Committee

**Dr. L. Jeyaseelan, MSc, PhD**
Secretary, Research Committee, IRB

**Dr. Alfred Job Daniel, MS Ortho**
Chairperson, Research Committee & Principal

**Dr. Gagandeep Kang, MD, PhD, FRCPath**
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal(Research)


November 29, 2011

Dr. Smita Dikshit
PG Registrar
Department of Ophthalmology
Christian Medical College
Vellore 632 004

Sub: **FLUID Research grant project NEW PROPOSAL:**
A randomized controlled clinical trial to compare the efficacy of intraoperative mitomycin C and Ologen implantation in patients undergoing phacoemulsification with trabeculectomy.
Dr. Smita Dikshit, PG Registrar, Ophthalmology, Dr. Andrew Braganza, Dr. Lekha Mary Abraham, Dr. Arathi Simha R

Ref: IRB Min. No. 7689 dated 23.11.2011

Dear Dr. Dikshit

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A randomized controlled clinical trial to compare the efficacy of intraoperative mitomycin C and Ologen implantation in patients undergoing phacoemulsification with trabeculectomy" on November 23, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Consent Form (English, Tamil and Hindi)
3. DCGI letter dated 24.12.2009
4. Cvs of Drs. Smita Dikshit, Andrew Braganza, Lekha Mary Abraham, Arathi Simha R
5. A CD containing document 1 – 4

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on November 23, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.


TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

# INSTITUTIONAL REVIEW BOARD (IRB)
# CHRISTIAN MEDICAL COLLEGE
## VELLORE 632 002, INDIA


**Dr. George Thomas, D Orth**
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**Dr. Gagandeep Kang, MD, PhD, FRCPath**
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal(Research)


| Name | Qualification | Designation | Other Affiliations |
|---|---|---|---|
| Dr. Prabhakar D Moses ( on behalf of Dr. Lionel Gnanaraj) | MBBS, MS, M.Ch. (Urol) | Medical Superintendent, CMC. | |
| Dr. Prathap Tharyan | MD, MRCPsych. | Associate Director, Professor of Psychiatry, CMC | |
| Mrs. Mary Johnson (on behalf of Mrs. Dr.Jayarani Premkumar) | M.Sc. (Nursing) | Nursing Superintendent, CMC. | |
| Mrs. Shirley David (on behalf of Mrs. Rosaline Jayakaran) | M.Sc. (Nursing), RN, RM | Dean, College of Nursing, CMC. | |
| Rev. Malhia Joshua | MA, MEd, MTh, PhD | Chaplain, CMC | |
| Mr. Harikrishnan | BL. | Lawyer | Non-CMC |
| Dr. Sujith Chandy | MBBS, MD | Professor, Pharmacology Dept. CMC. | |
| Mrs. S. Pattabiraman | BSc, DSSA | Social Worker, Vellore | Non-CMC |
| Dr. P. Zachariah | MBBS, PhD | Retired Professor , Vellore | Non-CMC |
| Dr. Gagandeep Kang | MD, PhD, FRCPath. | Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), C | |

We approve the project to be conducted as presented.

The Institutional Review Board expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

A sum of ₹ 80,000/- (Rupees Eighty thousand only) is sanctioned for 2 years.

Yours Sincerely

L. Jeyaseelan

Dr. L. Jeyaseelan, Ph.D.
Secretary (Research Committee),
Institutional Review Board

SECRETARY,
Institutional Review Board
(Research Committee)
Christian Medical College,
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## APPENDIX B- INFORMATION SHEET IN ENGLISH

Christian Medical College, Vellore
Department of Ophthalmology

**A randomized trial to compare the safety & efficacy of Ologen & Mitomycin in combined cataract & glaucoma surgery**

INFORMATION SHEET

Following glaucoma surgery there is scarring at the wound site which can cause failure of surgery.

Conventionally Mitomycin drops are used during glaucoma surgery which is known to reduce this scarring process and hence increase the success rate. But rarely it can be associated with complications like severe decrease in intraocular pressure & infection leading to loss of vision. It is being routinely used for all glaucoma surgeries.

Ologen is a new implant which is placed over the wound which also decreases this scarring process and has been shown to be effective in a few studies. There are no serious complications associated with this implant over the last 10 years experience. Therefore we intend to compare these two methods of glaucoma surgery.
Ologen currently costs Rs.5000 compared to Rs.50 for Mitomycin.

Before surgery all patients will undergo regular investigations & examinations required for combined cataract and glaucoma surgery. They will be randomly divided into 2 groups- one receiving Mitomycin and the other receiving Ologen.
Information for the use of the study will be obtained during the patient's regular follow up visits on day 1, week 1, 6 weeks and 3 months as is usual for glaucoma surgery. Besides obtaining data, patients will be evaluated to determine if they require other additional treatments for maintaining intra-ocular pressure like sub-conjunctival injections, needling and laser treatment.

The complications associated with combined cataract and glaucoma surgery include infection, irritation, repeat surgeries, inflammation, very low intra-ocular pressure, prolonged stay.

All patient details will be kept confidential.
In case of any problems or questions, you may contact Dr. Smita Dikshit at 9789551261.There are totally 60 patients in the study, and findings of the study will be accessible to the investigator at the end of 12 months.

## APPENDIX C - CONSENT IN ENGLISH

## CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: Randomised , double blinded, active controlled, clinical trial to compare the effect of Mitomycin & Ologen implant in phacotrabeculectomy.

Study Number: Subject's Name:

Date of Birth / Age:_____

(Please tick boxes)

I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I agree to take part in the above study. [ ]

Name: Name of witness:

Signature/ thumb print : Relation to participant:

Date: Signature:

**APPENDIX D- INFORMATION SHEET IN TAMIL**

## கிருஸ்தவ மருத்துவக் கல்லூரி. வேலூர்.
## கண் துறை

"ஒருங்கிணைந்த விழி புரை நீக்கம் மற்றும் விழி உள் நீர் அழுத்த அறுவை சிகிச்சை முறையில் ஒலோஜன் மற்றும் மைட்டோமைசின் ஆகியவற்றின் வேறுப்பட்ட தன்மைகள் குறித்த ஆய்வு".

### தகவல் தாள்

விழி உள் நீர் அழுத்தம் (Glaucoma) குறைய செய்யப்படும் அறுவை சிகிச்சையின் போது ஏற்படும் சிறு காயத்தினால் அறுவை சிகிச்சை தோல்வியாகிறது.

இதனை தடுப்பதற்கு வழக்கமாக மைட்டோமைசின் சொட்டு மருந்து உபயோகப்படுத்துவதின் மூலம் இந்த அறுவை சிகிச்சை தோல்வி தவிர்க்கப்படுகிறது. வெகு அறிதாக இச்சொட்டு மருந்தினால் விழி உள் நீர் அழுத்தம் குறைதல் பார்வை குறைவு மற்றும் தொற்று ஏற்படுதலுக்கு வாய்ப்பு உள்ளது.

கடந்த 10 வருடங்களாக ஹோலோஜன் பொருத்துவதன் மூலம் மேற்சொன்ன குறைபாடுகள் தவிர்க்கப்படுவதாக இது குறித்த சில ஆய்வு அறிக்கைகள் கூறுகின்றன. எனவே இவ்விரு முறைகளையும் ஒப்பிட்டு பார்க்கும் படியாக இந்த ஆய்வு நடத்தப்படுகிறது.

ரூபாய் 50/- க்கு செலவாகும் மைட்டோமைசினை ஒப்பிட்டு பார்க்கும் போது ஹோலோஜன் (Ologen) பொருத்துவதற்கு ரூபாய் 5000 செலவாகிறது.

ஒருங்கிணைந்த புரை மற்றும் விழி உள் நீர் அழுத்த அறுவை சிகிச்சைக்கு தேர்வு செய்யப்படும் நோயாளிகளுக்கு சில பரிசோதனைகளும் சிறப்பு ஆய்வுகளும் செய்யப்படும். இதன் மூலம் தெரிவு செய்யப்பட்டவர்கள் இரு பிரிவாக மைட்டோமைசின் சிகிச்சைக்காகவும் ஹோலோஜின் சிகிச்சைக்காகவும் பிரிக்கப்படுகின்றனர்.

இந்த ஆய்வு குறித்த தேவையான தகவல்களை நோயாளி இந்த மருத்துவமனைக்கு வரும் முதல் நாள் முதல் வாரம் ஆறாம் வாரம் மற்றும் 3 -ம் மாதம் ஆகிய வருகையின் போது திரட்டப்படுகிறது. இககால கட்டத்தில் விழி உள் அழுத்தம், லேசர் மற்றும் வெண் திரையில் ஏற்படும் சோய்கள் குறித்தும் மதிப்பிடபடுகிறது.

ஒருங்கிணைந்த புரை மற்றும் விழி உள் நீர் அழுத்தம் அறுவை சிகிச்சையின் பிறகு தொற்று, எரிச்சல் மீண்டும் அறுவை சிகிச்சை மற்றும் நீண்ட நாள் மருத்துவமனையில் தங்க வேண்டிய கட்டாயம் ஏற்படுகிறது. நோயளிகள் குறித்த அனைத்து தகவல்களும் பத்திரமாக பாதுகாக்கப்படும்.

இச்சோதனையில் சுமார் 60 நோயாளிகள் இருக்கிறார்கள். இந்த ஆய்வு குறித்த முழுத் தகவல்களும் 12 மாதங்களுக்கு பிறகு தெரியவரும். மேற்கொண்டு தேவைப்படும் மற்ற தகவல்களுக்கு டாக்டர்.ஸ்மித்தா டிக்ஸித்தை 9789551261 என்ற எண்ணில் தொடர்பு கொள்ளலாம்.

## APPENDIX E- CONSENT SHEET IN TAMIL

"ஒருங்கிணைந்த விழி புரை நீக்கம் மற்றும் விழி உள் நீர் அழுத்த அறுவை சிகிச்சை முறையில் ஓலோஜன் மற்றும் மைட்டோமைசின் ஆகியவற்றின் வேறுப்பட்ட தன்மைகள் குறித்த ஆய்வு".

ஆய்வு எண் :

பிறந்த தேதி வயது : 46

..... அன்று எனக்கு கொடுக்கப்பட்ட தகவல் பிரிதியில் மேற்கூறிய ஆராய்ச்சி பற்றியும் அதைக் குறித்து கேள்விகளை கேட்கலாம் என்றும் அறிந்திருக்கிறேன்.

இதன் மூலம் நான் அறிந்து கொண்டது என்னவென்றால் இந்த ஆராய்ச்சியை நடத்துபவர்கள் எனது மருத்துவ பதிவேட்டை தற்பொழுது நடைபெறும் ஆராய்ச்சி மற்றும் வருங்காலங்களில் நடத்தப்படும் ஆய்வுகளுக்கும் பயன்படுத்தப்படும் என்று அறிந்திருக்கிறேன். இந்த ஆராய்ச்சியில் இருந்து நான் விலகினாலும் எனது அடையாளங்கள் வேறு யாருக்கும் தெரியப்படுத்தமாட்டாது என்று அறிந்திருக்கிறேன்.

ஆராய்ச்சி முடிவுகளை, ஆராய்ச்சி பயன்பாட்டிற்காக உபயோகிப்பதை நான் எவ்விதத்திலும் தடுக்கமாட்டேன்.

இந்த ஆராய்ச்சியில் பங்கு கொள்வதன் மூலம் எந்த இழப்பீடும் கிடைக்காது என்றும், ஆராய்ச்சி சம்பந்தமான ஏதேனும் காயம் மற்றும் விரும்பத்தகாத நிகழ்வுகள் ஏதும் ஏற்பட்டால் இலவச மருத்துவ உதவி மட்டும் கிடைக்கும் என்றும் புரிந்து கொண்டுள்ளேன்.

நான் இந்த ஆராய்ச்சியில் பங்கு பெற விருப்பம் தெரிவிக்கிறேன்.

பெயர் : R.Navaneetham சாட்சியின் பெயர் : A. [illegible]

கையோப்பம் கைரேகை : R.Navaneetham பங்காளரின் உறவு முறை : Daughter

தேதி : 13/6/2012 கையோப்பம் : A. [illegible]

# APPENDIX F– DATA COLLECTION PROFORMA

## RCT COMPARING PHACOTRABECULECTOMY WITH MMC VS OLOGEN

NAME: HUSBAND'S/FATHER'S NAME:
AGE/SEX: HOSPITAL NUMBER:
ADDRESS: PHONE NUMBER:
PATIENT SERIAL NUMBER: GROUP: MMC/ OLOGEN
DATE OF ENROLLMENT: DATE OF SURGERY:

**PREOPERATIVE EXAMINATION:**

| | **RIGHT** | **LEFT** |
|---|---|---|
| BCVA | | |
| RAPD | | |
| AC DEPTH | | |
| GRADING OF CATARACT | | |
| IOP | | |
| CCT | | |
| **GONIOSCOPY:** | | |
| IN SITU | | |
| OTH | | |
| ON MANIPULATION | | |
| **HFA:** | | |
| 30-2 | | |
| 24-2 | | |
| 10-2 | | |
| MACULAR PROGRAM | | |
| **FUNDUS:** | | |
| DISC SIZE | | |
| NRR | | |
| NFLD | | |
| DISC HEMOORRHAGES | | |
| MACULA | | |

| | | |
|---|---|---|
| ANTIGLAUCOMA MEDICATIONS | | |

**DIAGNOSIS:**

**TARGET IOP:**

**INTRAOPERATIVE COMPLICATIONS:**

**EYE OPERATED:**

**POSTOPERATIVE EXAMINATION:**

| | DAY 1 | WEEK 1 | WEEK 6 | 3 MONTH |
|---|---|---|---|---|
| DATE | | | | |
| VISION/BCVA | | | | |
| BLEB MORPHOLOGY | | | | |
| SEILDEL'S TEST | | | | |
| AC DEPTH | | | | |
| CELLS/FLARE | | | | |
| IOP | | | | |
| HYPHEMA | | | | |
| LENS | | | | |
| **FUNDUS:** | | | | |
| CHOROIDALS | | | | |
| HYPOTONIC MACULOPATHY | | | | |
| BLEBITIS/ENDOPHTHALMITIS | | | | |
| GONIOSCOPY | | | | |
| OTHERS | | | | |

**ADDITIONAL INTERVENTIONS:**

BLEB MASSAGE:

INJECTION 5 FU:

RELEASING RELASEABLE:

LASER SUTUROLYSIS:

NEEDLING:

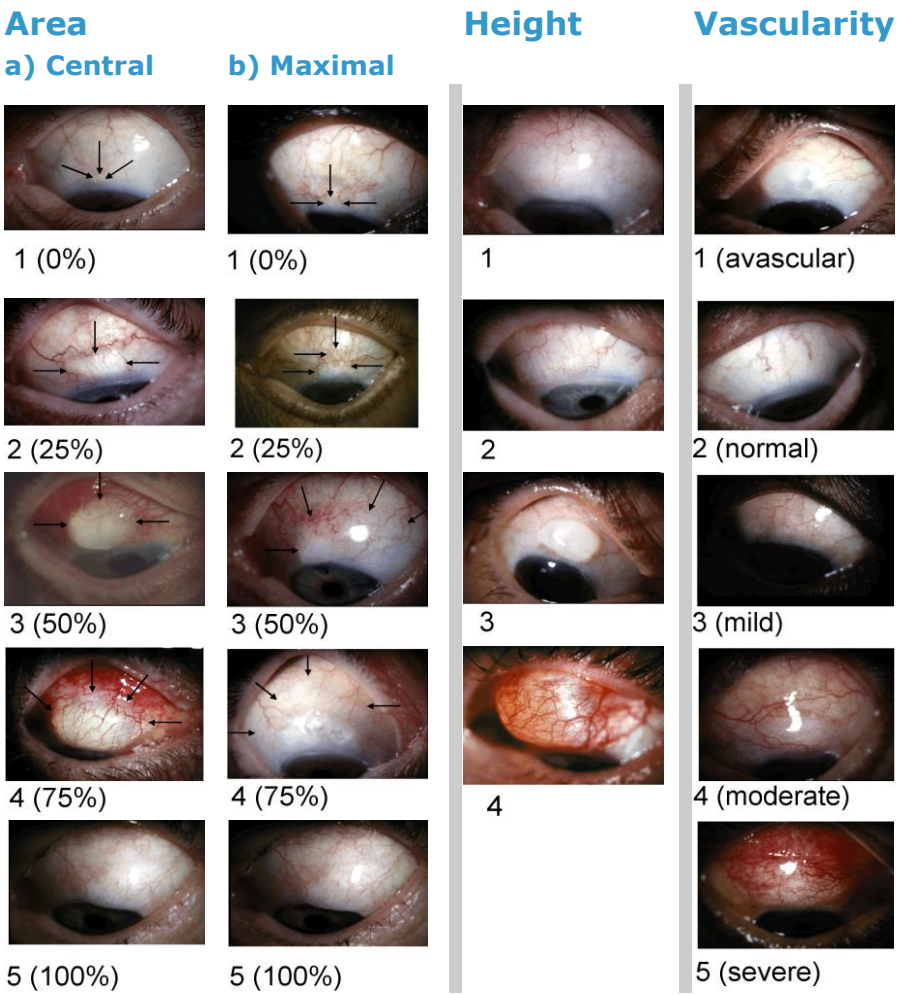
ANTIGLAUCOMA MEDICATIONS:

## MOORFIELD'S BLEB GRADING SYSTEM:

| | DAY 1 | WEEK 1 | WEEK 6 | 3 MONTH |
|---|---|---|---|---|
| DATE | | | | |
| **BLEB AREA** | | | | |
| CENTRAL DEMARCATED AREA; 1a | | | | |
| MAXIMAL AREA; 2a | | | | |
| **BLEB HEIGHT** | | | | |
| **BLEB VASCULARITY** | | | | |
| CENTRAL DEMARCATED AREA; 3a | | | | |
| MAXIMAL AREA; 3b | | | | |
| NON BLEB CONJUNCTIVA; 3c | | | | |
| SUBCONJUNCTIVAL BLOOD | | | | |
| TOTAL | | | | |

## APPENDIX G

**Figure 14: Moorfield's Bleb Grading System standard photographs**



## APPENDIX H – BLEB PHOTOGRAPHS WITH SCORING

**Figure 15: Area 2a with score 3 in a MMC bleb**

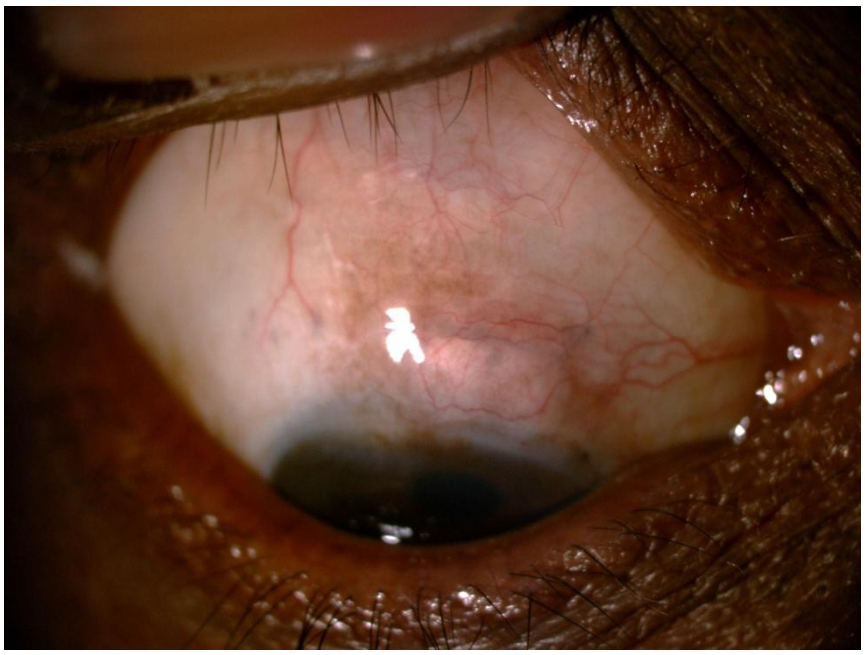


**Figure 16: Area 2a with a score 2 in Ologen bleb**

**Figure 17: Area 2 a with a score 3 in Ologen bleb**

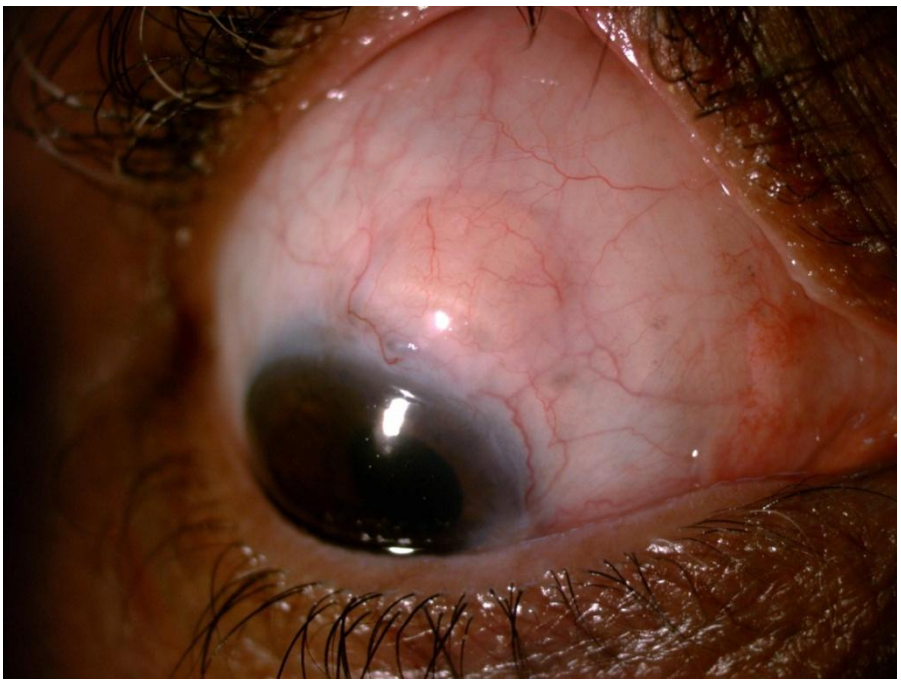


**Figure 18: Area 2a with score 4 in MMC bleb**

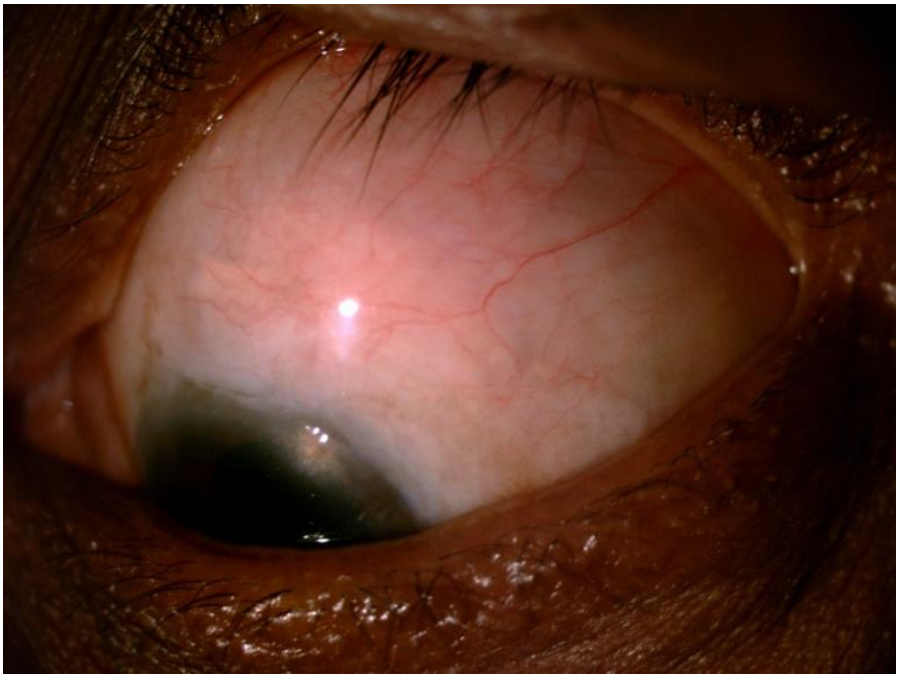


**Figure 19: Height score 2 in a MMC bleb**

**Figure 20: Height score 3 in Ologen bleb**

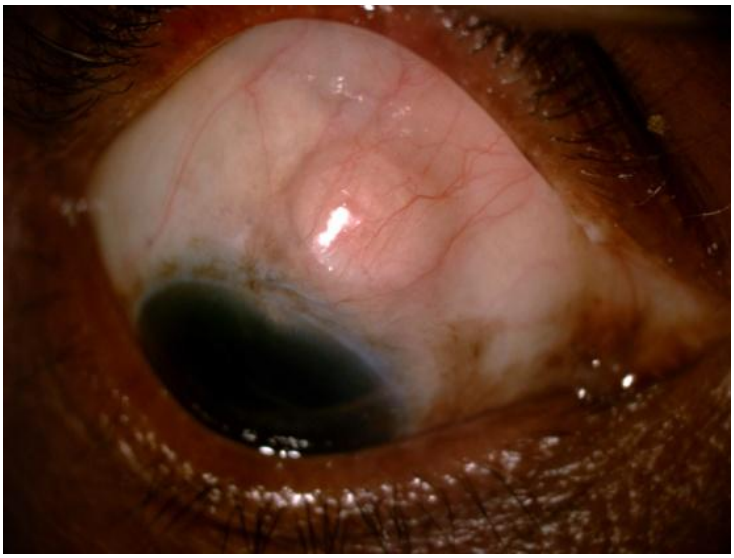


**Figure 21: Central demarcated area 3a with a vascularity score of 1 in a MMC bleb**

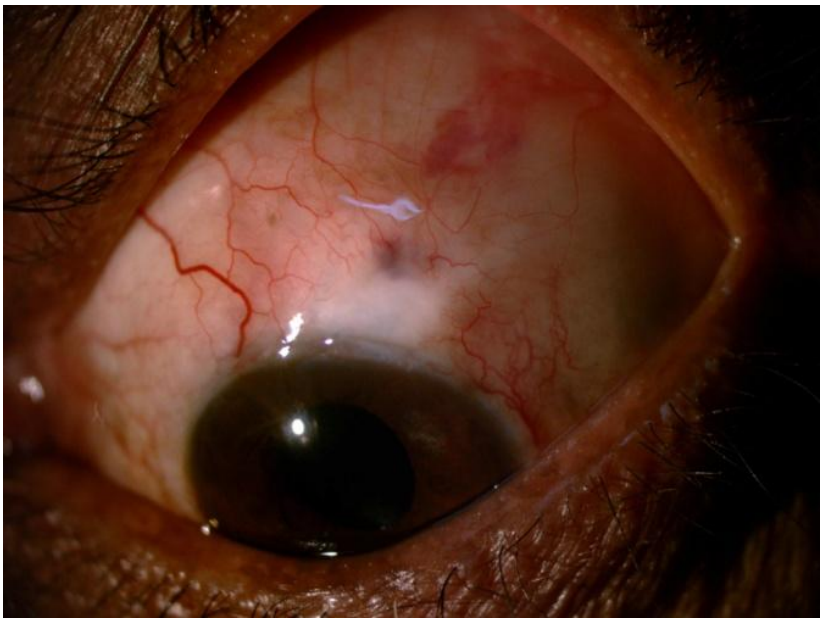


**Figure 22: Central demarcated area 3a with a vascularity score of 4 in Ologen bleb**

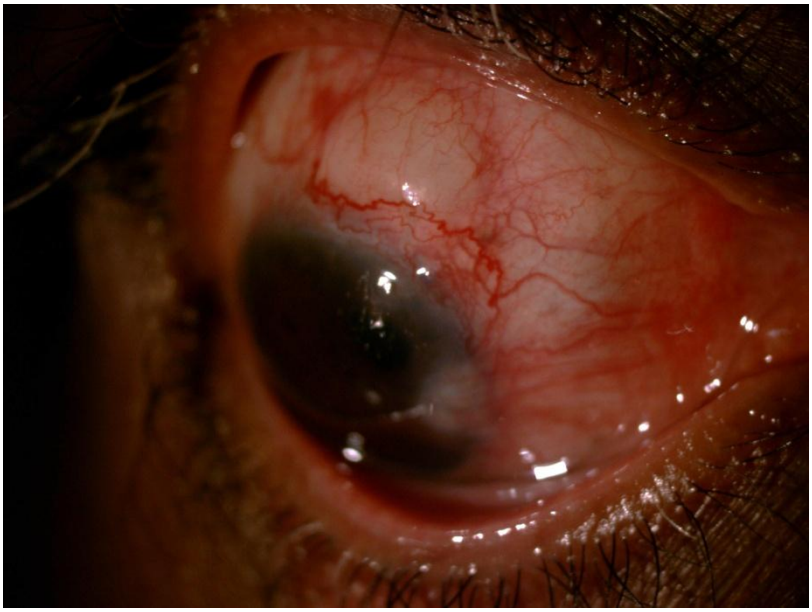


**Figure 23: Maximal area 3b with a vascularity score of 4 in Ologen bleb**

**Figure 24: Maximal area 3b with a vascularity score of 5 in Ologen bleb**

**Figure 25: Ologen bleb with subconjunctival haemorrhage**

**Figure 26: MMC bleb with subconjunctival haemorrhage**